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NUCLEOPHILIC ADDITION OF AMINES TO THE ACTIVATED ETHYLENE BOND

IV.* STRUCTURAL EFFECTS OF ALIPHATIC AMINES IN REACTIONS OF ADDITION TO TRANS-FURYL-NITROETHYLENE .

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Kinetics of addition of aliphatic amines to trans-furylnitroethylene in acetonitrile has been studied and rate constants of the non--catalytic (k) pattern and that of formation of the corresponding 2-(1-amino-2-nitroethyl) furan, catalyzed by the second molecule of the initial amine (k_b) have been determined. For primary amines, the rate constants of the amin nucleophilic attack on the trans-furyl-nitroethylene (k_1) were also found. In case of both reaction patterns (k and k_b) and in case of step k_1, the reactivity of amines is described by the modified Taft equation. On the basis of the obtained results, a conclusion has been made on the similarity of mechanism of interaction of primary and secondary amines in the process studied. In the transition state of the first stage of the reaction, a high C-N bond

* See [1] for report III.

formation level was observed. The E_N constant for methyl-n-butylamine (1.19±0.09) has been found.

The structural effect of aliphatic amines on their reactivity has been studied in case of their addition to the activated ethylene bond on the example of their interaction with acrylonitrile[2,3], acrylamide and acrylaniline[4], phenylvinylketone[5] and p-methoxyphenylvinylketone[3], as well as p-methylphenylsulfone[6]. In order to quantitatively estimate the simultaneous influence of the inductive and steric effects of the amine, equation (1), proposed already in[7], was used in the reactions of addition to the activated olefin:

$$\log k = \log k_o + \rho^{*} \Sigma\delta^{*} + \delta E_N \qquad (1)$$

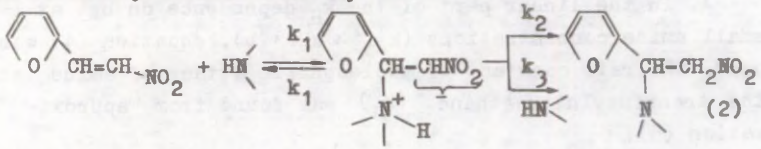
$\Sigma\delta^{*}$ characterizes the inductive substituent effect at the nitrogen atom, E_N is the steric accessibility of the atom, ρ^{*} and δ denote the reaction's susceptibility to these effects.

In all cases, the reactivity of the primary and secondary amines obeyed a common correlation dependence. The kinetics of the amines' addition to the substrates used was studied either in aqueous[2-4] or water-alcohol[3] media where the step-wise reaction mechanism whose rate is determined by the nucleophilic attack at the ß-carbon atom (relative to the activating group) of olefine is generally accepted.[8] The reaction has the first order, concerning each reagent.

In aprotic media such studies were not made. At the same time, as it was shown in [1,9,10] in the polar aprotic media alongside the noncatalytic reaction, the pattern catalyzed by the second molecule of the initial amine is observed. It is conditioned by the fact that in such a case the proton transfer stage is significant from the point of view of the total rate of the process and the second molecule of the initial amine functions as a general basic catalyst.

It was shown in our previous report[1] that in the reactions of aliphatic amines with trans-furylnitroethylene in

acetonitrile, the transition from the secondary amines to the primary ones brings about a change of the kinetic regularities of the reaction (the dependence of the observed second order rate constant on the amine concentration transforms from the linear to the hyperbolic one). Still, the analysis of the effect of various factors on the kinetics of the process leads us[1] to the conclusion about the existence of a common reaction mechanism (in case of the primary and secondary amines) (see Eq. (2)).



In order to confirm and to further specify the suggested[1] reaction mechanism, the structural effect of the amines on the rate of the noncatalytic reaction pattern and that catalyzed by the second molecule of the initial amine is studied in the present paper.

If the quasi-stationary principle is followed, Scheme (2) is transformed in case of the studied second order rate constant (k_H) into (3).

$$k_H = \frac{k_1(k_2 + k_3 \cdot b)}{k_{-1} + k_2 + k_3 \cdot b}, \qquad (3)$$

where b is the amine concentration.

For the secondary amines (within the measurable concentration range) the second order rate constant appears to be the linear function of the amine's concentration. It follows from Scheme (2) that such regularities are followed only if $k_{-1} \gg k_3 \cdot b$:

$$k_H = \frac{k_1(k_2+k_3 \cdot b)}{k_{-1} + k_2} = \frac{k_1 k_2}{k_{-1}+k_2} + \frac{k_1 k_3}{k_{-1}+k_2} \cdot b = k + k_b \cdot b; \qquad (4)$$

k and k_b are the rate constants of, respectively, the non-catalytic reaction pattern and of that catalyzed by the second amine molecule.

In the case of primary amines, the k_H dependence on b is, generally, of hyperbolic shape but Eq.(4) holds at small amine concentrations, only. In Scheme (2), it means that $k_{-1} \approx k_3 \cdot b$ and the studied second order rate constant is described by (3). In order to determine the k, k_b and k_1 constants, two methods (see[1]) were applied.

A. In the linear part of the k_H dependence on b, at small amine concentrations ($k_{-1} \gg k_3 \cdot b$), equation (4) was used. The rate constant of nucleophilic attack of amine at the transfurylnitroethane (k_1) was found from approximation (5):

$$\frac{1}{k_H - k} \approx \frac{1}{k_1} + \frac{1}{k_b} \cdot \frac{1}{b} \qquad (5)$$

B. Dependence (3) was turned polylinear (6) and treated according to the linear regression methods.

$$k_H = k + k_b \cdot b - \frac{k_b}{k_1} (k_H \cdot b) \qquad (6)$$

For a majority of amines, the results obtained according to the both methods coincide well[1]. With sterically complicated amines (tert.-butyl amine, tert.-octylamine), method B was applied, since in this case, it is difficult to satisfy the condition $k_{-1} \gg k_3 \cdot b$ experimentally and, on the other hand, calculation according to Eq. (5) leads to remarkable errors (approximation (5) yields satisfactory results only if $k_1 \geqslant 10\ k$ (see[1])).

The found k, k_b and k_1 constants (Tables 1 and 2) were treated according to Eq. (1). The data of Table 3 show (series 1 and 4) that the reactivity of amines of the both patterns (k and k_b) well obey dependence (1).Exclusion of a more strongly deviating point for cyclohexylamine leads to the better statistical correlation (series 2 and 5). It should be mentioned that if the $\sum \sigma^* = 0.62$ suggested in[13]

Table 1

Rate Constants of Addition of Secondary Amines to Trans-Furyl-Nitroethane in Acetonitrile at 25°C [a]

No	Amine	$b \cdot 10^2$ [b], M	k, $M^{-1} \cdot s^{-1}$	k_b, $M^{-2} \cdot s^{-1}$	$\varepsilon \cdot 10^2$	r	N [c]	$\sum\sigma^{*}$ [11]	E_N [11]
1	Piperidine	0.18-1.41	1.02±0.05	392±7	7.8	0.999	9	0.31	-0.79
2	Hexamethylene-imine	0.7-3.7	0.472±0.035	20.7±1.6	4.2	0.986	7	0.29	-1.10
3	Dimethylamine	0.15-2.47	0.282±0.012	106±1	1.7	1.000	6	0.49	-0.47
4	Diethylamine	5.5-21.9	0.192±0.005	0.763±0.031	0.65	0.992	12	0.29	-1.98
5	Di-n-butyl-amine	1.8-14.3	0.129±0.001	0.305±0.010	0.11	0.997	8	0.23	-2.04 [d]
6	Methyl-n-propylamine	0.36-8.7	0.224±0.008	11.9±0.2	1.7	0.999	12	0.37	-1.07 [d]
7	Methyl-n-butylamine	0.28-9.0	0.238±0.009	15.2±0.2	2.0	0.999	9	0.36	
8	Morpholine	0.22-14.0	0.0720±0.0008	12.39±0.15	2.2	0.999	15	0.62 [e]	-0.79 [e]

[a] Calculated according to Eq. (4). [b] Variation range of amine concentration. [c] N-Number of kinetic curves. [d] Taken from [12]. [e] Taken from [13].

Table 2

Rate Constants of Addition of Primary Amines to trans-Furylnitroethylene in Acetonitrile at 25°C

No	Amine	$b \cdot 10^2$, M [a]	$k \cdot 10^3$, $M^{-1} \cdot s^{-1}$	k_b', $M^{-2} \cdot s^{-1}$	k_1 [b], $M^{-1} \cdot s^{-1}$	N [c]	Method [d]	$\Sigma\sigma^*$ [11]	E_N [11]
1	Methylamine	0.18-8.5	43.2±12.2	27.1±1.1	6.47(26.5%)	11	A	0.98	-0.07
2	Ethylamine	0.14-15.4	62.1±4.1	10.2±0.2	3.56(6.6%)	26	B	0.88	-0.36
3	n-Propylamine	0.34-28.8	55.3±3.7	8.33±0.28	2.63(7.1%)	10	A	0.86	-0.39
4	iso-Propylamine	0.8-56	42.3±2.7	1.77±0.04	0.706(4.0%)	32	B	0.79	-0.93
5	n-Bytylamine	0.3-19	60.5±2.4	9.02±0.11	3.74(7.5%)	18	A	0.85	-0.40
6	iso-Butylamine	1.25-20.0	38.2±3.8	3.72±0.09	4.31(14.9%)	10	B	0.86	-0.35
7	tert-Butylamine	8.5-137	16.8±0.1	0.0485 ±0.0012	0.0537(3.5%)	8	B	0.68	-1.74
8	Cyclohexylamine	0.6-73.5	45.6±2.4	2.17±0.05	0.903(2.9%)	27	B	0.83	-0.98
9	tert-Octylamine	11-88.4	7.08±0.07	0.0087±0.0011	0.0171(21.6%)	6	B	0.68[e]	-1.91[e]
10	Allylamine	0.6-74	8.86±0.68	1.15±0.01	1.13(3.0%)	25	A	1.14[e]	-0.2[e]
11	Benzylamine	1.0-31.5	4.26±0.49	0.87±0.02	0.731(6.6%)	24	A	1.20	-0.38

[a] Variation range of amine concentration. [b] In parentheses are given relative standard errors when determining the $1/k_1$ and $1/k_b$ according to (5) and (6) (methods A and B), respectively. [c] N-is the number of kinetic curves. [d] See the text. [e] Taken from [12].

Table 3

Parameters of Correlation of Rate Constants of Aliphatic Amines with trans-Furylnitroethylene in Acetonitrile According to Eq. (1).

No	Correlated constant	log k_o	ρ^*	δ	s	R^a	N^a
1	k	1.26±0.18	-2.69±0.18	0.71±0.08	0.17	0.969	18
2	k^b	1.31±0.16	-2.76±0.16	0.74±0.07	0.15	0.977	17
3	k^c	2.00±0.47	-3.36±0.45	0.87±0.12	0.16	0.942	11
4	k_{b_b}	5.04±0.33	-3.71±0.32	2.21±0.15	0.30	0.968	18
5	k_{b_b}	5.13±0.30	-3.83±0.30	2.25±0.14	0.27	0.976	17
6	k_{b_b}	4.79±0.98	-3.47±0.95	2.17±0.25	0.33	0.959	11
7	k_{1_c}	3.20±0.47	-2.31±0.45	1.68±0.12	0.16	0.985	11
8	k_1	3.18±0.32	-2.31±0.31	1.71±0.08	0.11	0.994	10

[a] R-is the multiple correlation coefficient , N-is the number of amines.

[b] In series 2,5,8 cyclohexylamine is excluded, if compared with series 1,4,7.

[c] Treatment of data for primary amines (Table 2).

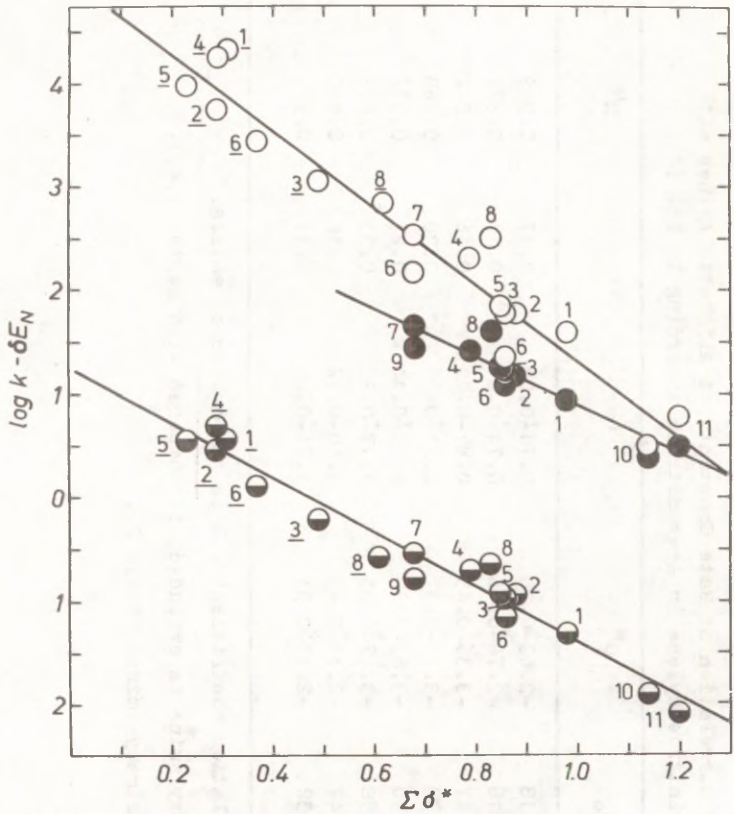


Fig. 1. Comparison of (log k - δE_N) values with those of $\Sigma\delta^*$ in case of amines' reactions with transfurylnitroethylene in acetonitrile at 25°, numeration corresponds to Tables 1 and 2 (the data of Table 1 are underlined).

◒ - noncatalytic reaction (log k - 0.71 E_N);
○ - catalytic reaction (log k_b - 2.21 E_N);
● - nucleophilic attack (log k_1 - 1.68 E_N).

is used, the morpholine term suits relationship (1) (in case of both patterns) (Fig. 1, term 8).

The steric constant for methyl-n-butylamine was calculated according to relationship (1) for the non-catalytic and catalytic reactions, using value $\Sigma\delta^{*}=0.36$. The E_N values found from series 2 and 5 coincide within the error range , equalling 1.27 ± 0.12 and 1.14 ± 0.07, respectively; the mean value is 1.19 ± 0.09.

Correlation treatment of the rate constants k and k_b according to Eq. (1) for the primary amines only (series 3 and 6) does not influence the values of the susceptibility parameters ρ^{*} and δ. Consequently, the reactivity of the primary and secondary amines obeys the general correlation dependence for both the noncatalytic and catalytic flows and agrees with the supposition about their common mechanism of addition to trans-furylnitroethane.

For the primary amines were also obtained the rate constants k_1 of the first stage of the reaction. It should be mentioned that peak values of the rate constants k_H formed 20-60% out of the k_1 values in case of the highest measurable concentrations of amine. Thus, as the k_1 value, found according to Eqs. (5) or (6) is a result of a rather distant extrapolation, therefore it should be quite susceptible to the selected extrapolation reaction. The fact that the k_1 values obey relationship (1), seems to refer to the correctness of the suggested[1] reaction mechanism (2), that of the equation of the process rate (3) and of the approach (see Eqs.(5)-(6)) for the calculation of constants. High absolute values of the coefficients ρ^{*} (-2.31) and δ (1.68) in case of the amine nucleophilic attack at transfurylnitroethylene evidence about a significant level of the C-N bond formation in the transition state of the first reaction stage (2). A similar conclusion was made in[10] on the bases of the influence of the medium polarity effect on the rate.

Experimental

Trans-furylnitroethylene[10], amines[1,10] and acetonitrile[9] were purified as described earlier. Kinetic measurements

were conducted spectrophotometrically (according to the substrate decrease λ = 350 nm) on an SF-26 under the pseudo-monomolecular conditions (in case of amine's excess). The methods of kinetic measuring and calculation of rate constants are given in[10].

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ULTRASONIC ACCELERATION OF GRIGNARD REAGENT FORMATION. A KINETIC STUDY.

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The kinetics of formation of n-butylmagnesium bromide in toluene in the presence of small additions of ethyl ether (from 0.17 to 0.68 mole to a mole of butyl bromide) with ultrasonic irradiation (44 kHz, 100 W) and without sonication was investigated. In ultrasonic conditions the induction period of the process is reduced considerably and the reaction rate is markedly increased. The rate constant of the slow step of the reaction increases nearly twice. The dependence of the reaction rate on the molar ratio of the ether, and the yield of Grignard reagent do not change under the influence of ultrasonic irradiation.

It is known that ultrasonic irradiation facilitates various chemical reactions, particularly those of heterogeneous nature[1]. So, irradiation with ultrasound was applied to accelerate the formation of some organometallic compounds, and also their reactions[2-9]. It has been reported that in the Grignard reagent preparation with ultrasound the induction period was essentially reduced, however, the yield of the reagent did not change.[10] Ultrasonic irradiation promotes Grignard reaction even in the presence of considerable amounts of

water and ethanol.[2,10] We are not aware of any more detailed, let alone the kinetic investigations of the ultrasound influence on the Grignard reaction.

We studied the effect of ultrasonic irradation on the kinetics of our model reaction of n-butylbromide with magnesium in toluene in the presence of small additions of ethyl ether (less than one mole to a mole of the halide)[11]. Such a model system was chosen in connection with the application of bases in catalytic amounts in case of the industrial organomagnesium syntheses,and,because in such conditions the reaction rate permits to investigate the kinetics by means of simple and reliable methods.

EXPERIMENTAL

Reagents and Solvents

Toluene, ethyl ether, and n-butylbromide were purified as described earlier[11].

Magnesium metal was used in the form of granules, from 1.6 to 2.5 mm in diameter.

Apparatus

The reaction was carried out in a tightly closed three-neck 30-ml flask. Agitation of the reaction mixture was performed by a mechanical stirrer. The speed of stirring was controlled with the voltage of driving electrical current. One of side necks of the flask was capped with a teflon stopper which was equipped with a silicon rubber disk.

As a source of ultrasound, a dispersor UZDN-2T was employed. Its conic ultrasound probe was immersed into the reaction mixture through the second sideneck of the flask.The probe made of titanium had on its end a round tip of 15 mm diameter. The device could operate at 22 and 44 KHZ , its nominal electrical energy output was 400 W.

Acoustic capacity of the set was determined by the sonication product Cl^- in a test mixture (0.15 M aqueous Solution of chloroacetic acid in an argon medium). The mean acoustic output under the conditions of kinetic experiment

proved to be about 100 W.

The reaction flask was placed into a glass vessel, whose temperature was kept constant by means of a thermostat U-10. The kinetic measurements were carried out at 30°C, which in ultrasound conditions was accomplished adjusting the temperature of the thermostat to 20°C. The thermal equilibrium of the system was reached in a few minutes after the ultrasound irradiation had been switched on.

Kinetic Measurements.

Before the kinetic runs, 4.0 g of magnesium (0.165 g-atom, total surface about 70 cm^2) were placed into the reaction flask. The appropriate amounts of toluene and ethyl ether (altogether 20.0 ml in each run) were introduced into the flask by means of the calibrated pipets. The stirring, and if required, the ultrasound irradiation were switched on and when the system had reached a constant temperature, 3.0 ml of butyl bromide (0.028 g-mole) was introduced through the silicon rubber disk by a hypodermic syringe.

During the reaction at appropriate time intervals the 1.0 ml aliquots were drawn and analyzed acidimetrically to find the content of basic magnesium. If necessary, in the same aliquots the amount of halide was determined by the Volhard method.

R E S U L T S A N D D I S C U S S I O N

In order to elucidate the effect of ultrasound, the kinetic measurements were carried out in strictly similar conditions both with sonication and without the latter . As the preliminary experiments had not revealed any considerable effect of sonication at 22 KHZ, in further work 44 KHZ was employed only.

It is known[11] that in the case of organic base content less than one mole to a mole of organic halide, the Grignard reaction proceeds in a stepwise manner. The induction period of varied duration is followed by a rapid stage with formation of the monosolvated Grignard reagent . After that takes

takes place a slow reaction of zero-order kinetics, evidently catalyzed by a solvated organomagnesium compound.

Ultrasonic irradiation exerts a markedly accelerating effect on all the steps of the reaction. As already noticed earlier[10], most essentially reduces the length of the induction period. In our experiments with molar ratios of ether-butyl bromide from 0.17 to 0.68 under sonication the reaction was initiated without any induction period.In absence of ultrasound the induction period lasted from 5 min (molar ratio 0.68) up to 3 h (molar ratio 0.1).

It is seen from Fig. 1 that the rates of both steps of the reaction with ultrasonic irradiation are noticeably greater than without sonication. It is worth mentioning that the final yield of the Grignard reagent does not increase with irradiation. In Table the data for zero-order

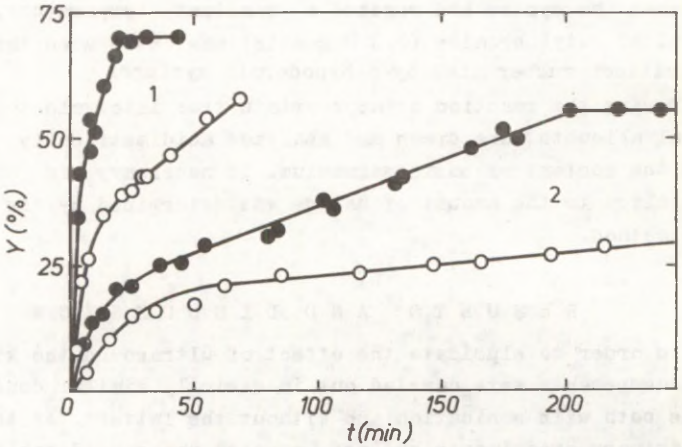

Fig. 1. The time-dependence of the yield of Grignard reagent with sonication (●) and without sonication (o) at molar ratios of ether to bromide: 1 -0.51; 2 - 0.34. The induction period is omitted.

Table

Rate Constants of the Slow Step of the Reaction (k_1 mole · l^{-1} · sec^{-1}) Without Sonication and With Ultrasonic Irradiation (44 KHZ, 100 W) at 30°C

Relative content of ether	$k \cdot 10^4$	
	with sonic.	without sonic.
0.17	0.114±0.007	0.371±0.047
	0.123±0.009	0.378±0.028
		0.389±0.013
0.34	0.450±0.011	0.672±0.002
	0.548±0.024	0.674±0.019
		0.848±0.045
0.51	1.06 ±0.20	2.42 ±0.24
	1.26 ±0.21	2.59 ±0.14
0.68	2.71 ±0.30	4.47 ±0.25

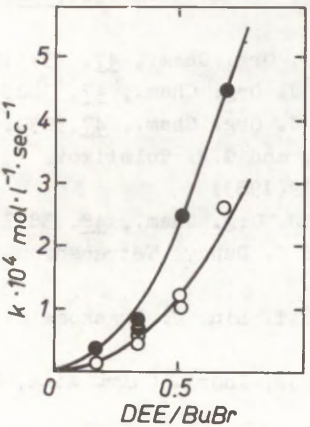

Fig. 2. Dependence of the rate constant of slow stage of the reaction on molar ratio of ether and butyl bromide without sonication (○) and with sonication (●).

reaction rate constants are given. It appears that the values of the rate constants at sonication are about twice higher than without irradiation. However, the dependence of rate constants on molar ratio ether-halide remains of the same quadratic type that we have found earlier[11] (Fig. 2).

The same yield of butylmagnesium bromide with sonication and in absence of ultrasonic irradiation, and the results of determinations of the content of magnesium bromide in the reaction mixture show that in these reaction conditions the ultrasonic irradiation does not influence the relative rates of formation of the Grignard reagent and the Würtz-type products. It follows that the ultrasonic irradiation of the given power can not change the mechanism of the Grignard reaction, however it favors the heterogeneous interaction of organic halide with the surface of magnesium metal.

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SOLUBILIZATION ALTERS COOPERATIVITY OF ANTAGONIST BINDING TO MUSCARINIC RECEPTORS

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Kinetics of L-[^{3}H] quinuclidinylbenzilate binding with solubilized muscarinic receptor from rat cerebral cortex was studied in 0.05 M K-phosphate buffer containing 0.3% digitonin (pH 7.40, 25°C). Under the excess of the ligand the pseudo-first-order rate constants k_{obs} were determined at 0.7 - 19.1 nM antagonist concentrations. The plot of k_{obs} vs antagonist concentration yielded a hyperbolic dependence pointing to the two-step reaction mechanism of the binding process, involving rapid complex formation followed by a slow conformational "isomerization" of the complex. The rate of the latter process cannot be regulated cooperatively, as has been found out in the case of the membrane-bound muscarinic receptor of rat brain. Moreover, the rate of the receptor-antagonist complex isomerization process is remarkably lower if compared with that of the membrane-bound receptor. The results obtained point to the important

role of the lipid environment of the receptor protein in determining its conformational mobility and cooperativity of the ligand-binding sites.

Cooperative regulation of the binding rate of potent antagonists L-quinuclidinylbenzilate and N-methylpiperidinylbenzilate with muscarinic receptors from rat brain gives evidence of the coexistence of several integrated ligand binding sites of the receptor[1,2]. These results point to the complex structure of the membrane-bound muscarinic receptor, probably consisting of several subunits interacting with each other. In the present paper the role of the lipid environment of this receptor complex in providing cooperative regulation of the antagonist binding rate has been studied. For the purpose a kinetic analysis of L-[^{3}H] quinuclidinylbenzilate binding to solubilized muscarinic receptor was carried out. The protein component responsible for the specific interaction of brain membranes with muscarinic ligands was extracted from its lipoprotein environment by digitonin, described previously as the most effective detergent for solubilization of the native muscarinic receptor[3].

Experimental

The procedure of preparation of the suspension of the membrane-bound muscarinic receptor in 0.05 M K-phosphate buffer, pH 7.40, has been described previously[4]. A detailed description of receptor solubilization with digitonin (Merck, No. 3193823) has been given in[3]. After treatment with 0.3% digitonin solution the membrane fragments were removed by centrifugation at 100 000 g during 60 min (K 32 M, USSR) and the components in the supernatant were considered to have been solubilized. This supernatant was used for kinetic measurements without any additional fractionation.

The receptor was assayed by the specific binding of L-[^{3}H] quinuclidinylbenzilate (specific radioactivity 38 Ci/mmol , "Amersham", England). The radiochemical purity of this ligand was tested by means of TLC on "Silufol 254 UV"

plates, using a chloroform-methanol mixture (9:1) as eluent. The amount of the radioligand bound with the solubilized receptor was determined by separating the receptor-ligand complex from the excess of the free ligand on Sephadex G50 columns as described previously[3].

Kinetic experiments were carried out in 0.05 M K-phosphate buffer, pH 7.40, 25°C. In order to stop the reaction of complex formation, a large excess of unlabelled quinuclidinylbenzilate was added into the reaction medium at appropriate time points. The unlabelled ligand was a generous gift from drs. N.N. Godovikov and N.A. Kardanov, Institute of Heteroorganic Chemistry, AS of the USSR, Moscow. The excess of unlabelled quinuclidinylbenzilate considerably dilutes the radioactive ligand, decreasing its specific radioactivity. This prevents any further incorporation of radioactivity into the protein fraction. Owing to the very slow dissociation rate of L-quinuclidinylbenzilate-receptor complex[3] the effect of displacement of the radioligand from this complex is negligible during the time interval needed for gel filtration of the samples.

Kinetic studies were carried out under the pseudo-first-order conditions involving an excess of the antagonist and the kinetic curves obtained were described by the rate equation for the first-order reaction[5]:

$$B_t = B_{ns} + B_{sp}(1 - e^{-k_{obs} \cdot t}) \qquad (1)$$

where B_t is the total radioactivity bound with the protein fraction at time moment t, B_{sp} - equilibrium specific binding, and B_{ns} - nonspecific binding of the radioligand. The value of B_{ns} was found from separate experiments in the presence of a large excess of non-radioactive quinuclidinylbenzilate (10 μM) or atropine (100 μM, Serva, FRG). It was established that the maximal level of the non-specific binding had been achieved before the first sample was taken from the reaction mixture and its value remained constant during the experiment.

The B_t values were calculated from the gel-filtration data as described previously[3]. The processing of the experi-

mental data was performed on "Nord-100" and "Commodore Plus 4" computers using the non-linear least squares programmes.

Results and Discussion

Addition of L-[^{3}H]quinuclidinylbenzilate into the receptor preparation results in an exponential increase in the protein-bound radioactivity that corresponds to the formation of the receptor-ligand complex (Fig. 1). The B_t vs t plots could be satisfactorily fitted to Eqn. 1 that allowed the calculation of the values of k_{obs}, B_{ns} and B_{sp}. The parameter B_{ns} in Eqn 1 characterizes the non-specific binding

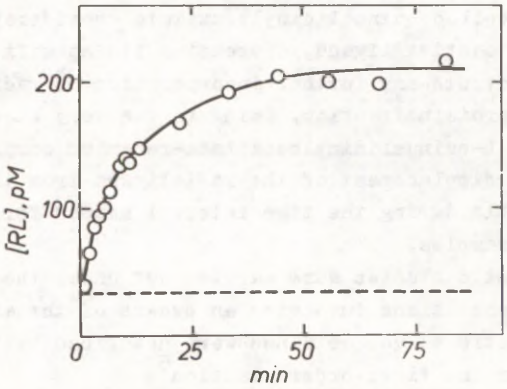

Fig. 1. Kinetics of binding of L-[^{3}H]quinuclidinyl benzilate to the solubilized muscarinic receptor from rat brain. (0.05 M K-phosphate buffer, 0.3% digitomin, pH = 7.4, 25°C). Concentrations of receptor sites and the ligand are 170 pM and 6.7 nM, respectively. The dotted line denotes the level of non-specific binding.

of the radioligand to the components that eluate from the Sephadex G50 column together with the solubilized receptor. Besides the non-specific binding of the radioligand to proteins its inclusion into the micelles formed by the detergent and lipid molecules should also be taken into account.

It was found that the amount of non-specifically bound radioligand depends upon the concentration of L- ^{3}H quinuclidinylbenzilate in the reaction medium.

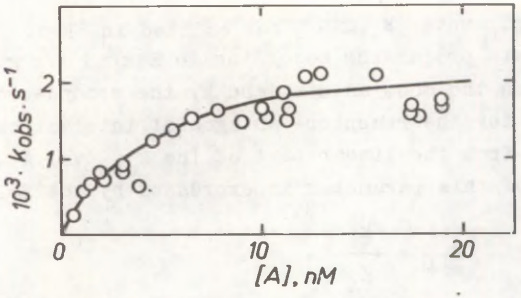

Fig. 2. Dependence of the binding rate constant k_{obs} on the concentration of L- ^{3}H quinuclidinyl benzilate for the solubilized muscarinic receptor from rat brain.

The plot k_{obs} vs antagonist concentration in the reaction medium yields a hyperbolic dependence (Fig. 2). The simplest reaction scheme to describe such results involves two consecutive equilibria[5]:

$$R + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RA \underset{k_{-i}}{\overset{k_i}{\rightleftharpoons}} (RA) \qquad (2)$$

the first and rapid step of complex formation is followed by a slow "isomerization" equilibrium. Assuming that only the slowly dissociating complex (RA) can be detected by the filtration method, the observed rate constant k_{obs} depends upon antagonist concentration as follows[6]:

$$k_{obs} = \frac{k_i [A]}{K_A + [A]} + k_{-i} \qquad (3)$$

where

$$K_A = \frac{k_{-1}}{k_1}$$

As the dissociation rate of the complex (RA) is much lower than the observed ligand binding rates ($k_{obs} \gg k_{-i}$), the values for k_{-i} could not be estimated on the basis of the experimental data shown in Fig. 2. Moreover, owing to the small value of $k_{-i} = 1.1 \cdot 10^{-5}$ s^{-1} found from independent experiments[3], the parameter k_{-i} can be omitted in Eqn. 3. The results of data processing according to Eqn. 3 are given in Table. Besides the constants K_A and k_i the second-order rate constant k_{II} for the receptor- antagonist interaction was also estimated from the linear part of the k_{obs} vs A plot. The meaning of this parameter is expressed by the following equation:

$$k_{II} = \frac{k_i}{K_A} \qquad (4)$$

It can be seen from the data in Table that the k_{II} value is in good agreement with the ratio of the constants k_i and K_A obtained from data processing by Eqn. 3.

Table

Kinetic Constants of Interaction of L -[^{3}H]-Quinuclidinyl Benzilate with the Muscarinic Receptor

Receptor preparation	K_A, nM	k_i, s^{-1}	k_{II}, $s^{-1}M^{-1}$	k_x, s^{-1}	K_x, nM
Solubilized receptor	3.8±0.8	(2.3±0.2)·10^{-3}	(4.7±1.0)·10^{-5}	-	-
Membrane-bound receptor	1.3±0.5	(1.2±0.3)·10^{-2}	(9.2±5.8)·10^{6}*	(1.8±0.2)·10^{-2}	4.4±0.8

* Calculated from the ratio of the constants k_i and K_A.

Comparison of the present results for the solubilized muscarinic receptor with the corresponding data for the membrane-bound receptor[1], clearly points to considerable differences between these two systems.

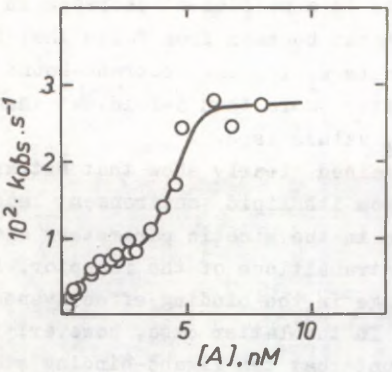

Fig. 3. Dependence of the binding rate constant k_{obs} on the concentration of L-[^{3}H] quinuclidinyl benzilate for the membrane-bound muscarinic receptor from rat brain, data taken from[1].

Fig. 3, reproducing the k_{obs} vs [A] plot for the membrane-bound receptor from a previous study shows that two inflection points are revealed in this dependence. The latter fact refers to the cooperative nature of the regulation of the ligand binding rate. By analogy with the Hill model, the cooperativity of the receptor system is characterized by a remarkably high value of the Hill coefficient n = 6 - 7 [1]. The meaning of this value can be illustrated in terms of the following reaction scheme[7]:

$$\begin{array}{ccccc} R & \rightleftharpoons & RA & \rightleftharpoons & (RA) \\ \downarrow\uparrow & & \downarrow\uparrow & & \downarrow\uparrow \\ A_nR & \rightleftharpoons & A_nRA & \rightleftharpoons & A_n(RA) \end{array} \qquad (5)$$

which assumes the binding of n additional ligand molecules to the receptor, resulting in acceleration of the isomerization step yielding the slowly dissociating complex (RA).

Besides the loss of the cooperative regulation of the rate of the receptor-ligand complex isomerization step, extraction of the muscarinic receptor from its membrane envi-

ronment also results in a sufficient decrease in the rate of this process. It can be seen from Table that the corresponding rate constants k_i for the membrane-bound and solubilized receptors differ more than 5-fold. At the same time the ratio of the K_A values is 2.9.

The results obtained clearly show that extraction of the receptor protein from its lipid environment leads to a remarkable alteration in the kinetic parameters characterizing the conformational transitions of the receptor. At the same time a certain change in the binding effectiveness of ligands is observed. In the latter case, however, it should be taken into account that the ligand-binding step can be interfered with by the detergent molecules probably covering the hydrophobic regions of the solubilized receptor protein.

In summary, the lipid environment of the membrane-bound muscarinic receptor of rat brain plays an important role in providing cooperative interaction between different ligand--binding sites. The loss of cooperativity of the muscarinic receptor as a result of its solubilization can be explained either by some remarkable conformational changes in the receptor protein or by destruction of its putatively aggregated structure consisting of several cooperatively integrated subunits. In the latter case the observed changes in the kinetic properties of the receptor can simply result from separation of these subunits by solubilization.

The need for differentiation between these alternative explanations calls for a more detailed analysis of the influence of the dynamic properties of the membrane on the effectiveness and kinetic parameters of ligand binding with the muscarinic receptor.

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QUANTITATIVE STATISTICAL INTERPRETATION OF KINETIC DATA IN THE GAS PHASE HOMOLYSIS

8. Program for Automatic Computational Estimation of Rate Constants of Gas Phase Homolysis and Heats of Formation of Covalent Compounds

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A program for computational estimation of free energies of activation and rate constants of the gas phase homolysis depending on the structure of radicals-substituents and on the temperature has been compiled. The program enables the calculation of heats of formation at 0 K for covalent compounds as well.

In the previous communications[1-7] of this series a possibility of the development and parametrization of the general enough calculation method on the ground of the formal-correlational approach is investigated for rate constants of the gas phase homolysis according to the scheme:

$$R_i - R_j \xrightarrow{k} R_i^{\cdot} + R_j^{\cdot} \qquad (1)$$

A list of substituent effects and their respective quantitative description has been presented for the given type of reactions. A calculation scheme for a computational estimation of heats of formation for covalent compounds in the gas phase at 0 K is also discussed[2].

One can examine the results obtained as a basis of the combined algorithm for calculation of the heats of formation and the rate constants of the gas phase homolysis depending on the different structure effects and temperature. For the purposes of automatic computation and first of all for automatic logical and search operations it is advisable to realize the algorithm described above as a program for a computer. We have compiled this program in the FORTRAN language for a "Nord-100" computer. The functioning of the program is based on the arrays of parameters for the radicals-substituents listed in Table 1. Besides, substituent effects for substituted groups $X_1X_2X_3C$ -, XO-, XN = N-, and XHg- can be taken into account.

1. Principled Scheme of Algorithm.

The results of papers[1-7] show that it is expedient to realize the calculation scheme in two main variants. The first of them formally corresponds to the isoentropic case with the universal value (A_o) of the preexponential factor (constant activation entropy[3-6]). In the second version the activation entropy is varied.

Obviously in case of wide temperature range and combinations of such radicals which have a large enough number of independent data the second version (taking into account the variation of entropy) must be more preferable. This is followed from the statistically proved modelling of the dependence of log A on the nature of radicals R_i and R_j as well as on the temperature in the result of inclusion of term log T. However, for the majority of radicals the reliable values of activation entropy ($\Delta S^{\neq}_{R\cdot}$) and the corresponding activation enthalpy ($\Delta H^{\neq}_{R\cdot}$) have not been found yet. In this case more reliable results can expectably be obtained according to the isoentropic model.

Computations for the estimation of the rate constants of the gas phase homolysis according to Scheme (1) may be realized according to the following concrete calculation schemes:

1.1. Groups R_i, R_j and the heat of formation of $\Delta H^{o}_{OR_iR_j}$ (DH12)* for compound R_i-R_j at 0 K are entered.

Energy (enthalpy) of activation E(EAKT) is calculated according to the formula:

$$E = \Delta H^{\neq}_{R_i\cdot} + \Delta H^{\neq}_{R_j\cdot} - \Delta H^{o}_{OR_iR_j}, \qquad (2)$$

at that the values either from Table 1 or calculated, taking into account substituent effects, if a corresponding equation is parametrized for the present type of substituted radicals, may be used as the $\Delta H^{\neq}_{R\cdot}$ values.

1.2. Groups R_i and R_j are entered but the value of the formation heat $\Delta H^{o}_{OR_iR_j}$ is not input (a fictitious value is entered). Calculations are carried out as follows:

$$E = \Delta\Delta H^{\neq}_{R_i\cdot} + \Delta\Delta H^{\neq}_{R_j\cdot} - I_{ij} \qquad (3)$$

where $\Delta\Delta H^{\neq}_{R\cdot} = \Delta H^{\neq}_{R\cdot} - \Delta H^{o}_{OR-}$, i.e. the differences between the heat of formation of a free radical and the additive enthalpy term for the corresponding substituent. The term I_{ij} represents the energy of intramolecular interaction between substituents R_i and R_j taking into account φ- and inductive contributions:

$$I_{ij} = \varphi_{R_i}\varphi_{R_j} + \alpha^{*}\sigma^{*}_{R_i}\sigma^{*}_{R_j} \qquad (4)$$

where φ_R are the substituent constants reflecting their ability to the φ-interaction (the scaling factor is equalized to 4.184 kJ/mol(1 kcal/mol)), σ^{*}_R are inductive substituent constants, α^{*} denote the scaling factor for the inductive interaction. Radicals $R_i\cdot$ and $R_j\cdot$ are again either those taken from Table 1 or the substituted ones of the types $X_1X_2X_3C^{\cdot}$, $XO^{\cdot}$, $XHg\cdot$ or $XN{=}N^{\cdot}$.

1.3. Besides the calculation of E according to Eqs.(2) or (3), the entropy of activation $\Delta S^{\neq}$ is calculated additively[7]:

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* Respective identifiers used in the program text are presented in parentheses.

$$\Delta S^{\neq} = \Delta S^{\neq}_{R_i\cdot} + \Delta S^{\neq}_{R_j\cdot} \qquad (5)$$

For the substituted methyls $X_1X_2X_3C\cdot$ the $\Delta S^{\neq}_{X_1X_2X_3C\cdot}$ values may be calculated as follows:

$$\Delta S^{\neq}_{X_1X_2X_3C\cdot} = \Delta S^{\neq}_{CH_3\cdot} + pY \qquad (6)$$

where Y is the parameter and p is the number of interactions between substituents X.

1.4. Parameters for free radicals $R^{\cdot}$ and their respective substituents R^- are listed in Table 1. For the substituted radicals of the types $X_1X_2X_3C\cdot$, $XO^{\cdot}$, $XN{=}N\cdot$, and $XHg\cdot$ the parameters of substituents R^- serve as the parameters for substituents X^-. Digital constants for the following values (see Table 1) have been assigned by DATA operators:

φ_R(FI) - φ-constants for substituents R^-

σ^{*}_R(SIGMA) - inductive constants for substituents R^-

$\Delta H_{R\cdot}$(DHRAD) - heats of formation of free radicals $R\cdot$ within the framework of the scheme using the universal value of $\log A_0 = 14.64$

(ERDHR) - their errors

$\Delta H^{\neq}_{R\cdot}$(DHSR) - heats of formation of free radicals taking into account the additive activation entropy

$\Delta\Delta H_{R\cdot}$(DDHRD) = $\Delta H_{R\cdot} - \Delta H_{RH}$

(ERDDH) - their errors

ΔH_{RH}(DHSBT) - additive increments for groups R^- of formation heats at 0 K

N_ψ(ANPSI) - resonance constants of substituents R^- for estimation of resonance interaction with the free-radical center

$\Delta S^{\neq}_{R\cdot}$(DDSR) - additive terms of the entropy of activation for radicals $R^{\cdot}$

1.5. For substituted methyl radicals ($X_1X_2X_3C\cdot$), substituted alkoxy radicals ($XO^{\cdot}$), alkyl substituted mercury radicals ($XHg\cdot$), and for the reactions of the homolytic dissociation of peroxides ($X_1O - OX_2$) and azo compounds it is

possible to estimate substituent effects using the following equations:

$$\Delta H^{\neq}_{X_1X_2X_3C\cdot} = \Delta H^{\neq}_{CH_3\cdot} + \sum_i \Delta H^{o}_{OX_i} + \varphi_{C\cdot}\sum_i \varphi_{X_i} + \alpha^{*}\sigma^{*}_{C\cdot}\sum_i \sigma^{*}_{X_i} + \alpha^{*} z^{*}_{C\cdot}\sum_{i<j}\sum \sigma^{*}_{X_i}\sigma^{*}_{X_j} + \psi_{=N=} + \psi_{CN}N_{CN} + \psi_{NO_2}N_{NO_2} \quad (7)$$

$$\Delta\Delta H^{\neq}_{X_1X_2X_3C\cdot} = \Delta\Delta H^{\neq}_{CH_3\cdot} + (\varphi_{C\cdot} - \varphi_{CH_3})\sum_i \varphi_{X_i} + 0.2\sum_{i<j}\sum \varphi_{X_i}\varphi_{X_j} - 0.02\varphi_{X_1}\varphi_{X_2}\varphi_{X_3} + \alpha^{*}\sigma^{*}_{C\cdot}\sum_i \sigma^{*}_{X_i} + \psi_{=N=} + \psi_{CN}N_{CN} + \psi_{NO_2}N_{NO_2} \quad (8)$$

$$\Delta H^{\neq}_{XO\cdot} = \Delta H_{X-} + \Delta H^{\neq}_{O\cdot} + \varphi_{O\cdot}\varphi_X + \alpha^{*}\sigma^{*}_{O\cdot}\sigma^{*}_X + \psi N \quad (9)$$

$$\Delta\Delta H^{\neq}_{XO\cdot} = \Delta H^{\neq}_{O\cdot} - \Delta H_{O-} + (\varphi_{O\cdot} - \varphi_O)\varphi_X + \alpha^{*}(\sigma^{*}_{O\cdot} - \sigma^{*}_O)\sigma^{*}_X + \psi N \quad (10)$$

$$E_{X_1O-OX_2} = 2\Delta H^{\neq}_{O\cdot} - \Delta H_{-OO-} + (\varphi_{O\cdot} - \varphi_{OO})(\varphi_{X_1} + \varphi_{X_2}) + \alpha^{*}(\sigma^{*}_{O\cdot} - \sigma^{*}_{OO})(\sigma^{*}_{X_1} + \sigma^{*}_{X_2}) + \alpha^{*}z^{*}_{OO}\sigma^{*}_{X_1}\sigma^{*}_{X_2} + \psi(N_{X_1} + N_{X_2}) \quad (11)$$

$$\Delta H^{\neq}_{XHg\cdot} = \Delta H_{X-} + \Delta H^{\neq}_{Hg\cdot} + \varphi_{Hg\cdot}\varphi_X \quad (12)$$

$$\Delta\Delta H^{\neq}_{XHg\cdot} = \Delta H^{\neq}_{Hg\cdot} - \Delta H_{-Hg-} + (\varphi_{Hg\cdot} - \varphi_{Hg})\varphi_X \quad (13)$$

$$E_{X_1-N=NX_2} = \Delta\Delta H^{\neq}_{X_1\cdot} + \Delta\Delta H^{\neq}_{N=N\cdot} + \varphi_{N=N\cdot}\varphi_{X_2} - \varphi_{N=N}(\varphi_{X_1} + \varphi_{X_2}) + \alpha^{*}\sigma^{*}_{N=N\cdot}\sigma^{*}_{X_2} - \alpha^{*}\sigma^{*}_{N=N}(\sigma^{*}_{X_1} + \sigma^{*}_{X_2}) - \alpha^{*}z^{*}_{N=N}\sigma^{*}_{X_1}\sigma^{*}_{X_2} \quad (14)$$

The parametrization of equations (7) and (8) is realized both in approximation of the effective mean value of the preexponential factor[6] and taking into account the variation of the activation entropy[7]. The other Eqs. (9)-(14) are so

far parametrized only in the framework of the isoentropic model and the results of their parametrization will be published separately.

1.6. In the case of the isoentropic approach (log A_o = = 14.64[3]) the logarithm of rate constant is calculated by the formula:

$$LGK = 14.64 - 1000E/(4.576\ T), \qquad (15)$$

where E is the energy of activation calculated according to Eq. (2) or (3), in kcal/mol, 4.576 = 2.3 R, T is temperature in K.

Within the framework of the scheme with the additive entropy of activation the logarithms of rate constants are calculated by the formula:

$$LGK = 10.319 + \log T + (\Delta S^{\neq} - 1000E/T)/4.576 \qquad (16)$$

where 10.319 = log (k/h)(the logarithm of relation of the Boltzmann and Planck constants), $\Delta S^{\neq}$ is the activation entropy according to Eq. (5) in entr. un.

2. Order of Preparation of Input Data

The above described algorithm is realized as a program in the FORTRAN-language for a "Nord-100" computer. The input data are moved in by video terminals on-line. However, the present version of the program may be easily transformed for other computers supplied with a FORTRAN translator.

Sequence numbers of free radicals R· and respective substituents R- are listed in Table 1. Up to ten separate jobs are solved in a single order. The following input data are moved in.

2.1. Total number of jobs N $\leqslant$ 10.

2.2. For each job five numbers are entered:

NVAR, I1, I2, T, and DH12

where NVAR is the selection constant for a variant of calculations, three values are accepted: 0, 1, and 2, I1 and I2 are numbers of order of radicals R_i and R_j from Table 1, T denotes the temperature in K, and DH12 is the heat of formation of compound R_i-R_j at 0 K

Depending on the NVAR values the next variants of the program run are realized:

NVAR = 0 - both R_i and R_j groups are entirely defined by their numbers of order I1 and I2 and calculation of substituent effects is not necessary,

NVAR = 1 - the group R_i (no. I1) belongs to a type with variable substituents(s) and in its case the effects of substituents must be calculated,

NVAR = 2 - the same concerns group R_j (no. I2).

If DH12 $\leqslant$ 999., this value is interpreted by program as the $\Delta H^{o}_{OR_iR_j}$ in kcal/mol and E is calculated according to Eq.(2). In the case of DH12 > 999 (it is convenient to input value 1000.) the $\Delta H^{o}_{OR_iR_j}$ value is not defined and calculations are carried out by Eq. (3).

2.3. If NVAR > 0 for the present job one must move in additional data concerning a detailed structure of the group R_i or the both groups R_i and R_j. For this purpose numbers of order I1 and I2 must have one of the following values:

2 - for substituted methyls $X_1X_2X_3C$-

66 - for groups of XO- type

85 - for groups of XN=N- type

104 - for groups of XHg - type

If I1 or I2 have the value of 104, saturated alkyl groups (hydrocarbon substituents) only may serve as substituents. The following additional input data are moved in for a detailed structure of group R:

NN

KO(J), KE(J), ISBJ(J), J = 2, ..., NN

where

NN is the total number of nonequivalent fragments and substituents taking into account also the first atom;

J is a number of order of a new, nonequivalent to the previous one, fragment or substituent differing from it by its position in molecule and by the no. in Table 1 (sequence number of the next in turn equivalence type),

KO(J) denotes the general smallest number of order for this fragment which is bonded to the present fragment or substituent,

KE(J) is the number of fragments or substituents equivalent to the present one (including also itself),

ISBJ(J) is the number of order of the substituent in Table 1.

For the first atom of the group J = 1 and the data for it are not moved in. If I1 or I2 = 85, the fragment N = N⁻ is considered as an effective first atom. If NVAR=1, a single table of these data is entered, while at NVAR=2 two tables are entered, for groups R_i and R_j, respectively.

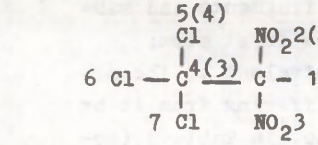
Carbon atoms - $\overset{|}{\underset{|}{C}}$ - (ISBJ = 2) only and the above indicated four centers as the first atoms can serve as substituted fragments.

Sequence numbers K for fragments or substituents are ascribed starting from the first atom of the group (K = 1) and further moving topologically away from this atom beginning with those which are bonded directly. Mutually equivalent fragments or substituents must be numbered successively.

Sequence numbers J for the equivalence types of fragments or substituents are attributed in the succession of increasing values of K, while the fragments or substituents being equivalent to the previous ones are omitted. Hydrogen atoms need not be showed.

Examples:

1) The structure of the group R = $CCl_3C(NO_2)_2^-$ could be taken to fragments and substituents as follows:



The values of sequence numbers K for fragments or substituents and, in parentheses , the sequence numbers J for equivalence types are indicated. The J values are not assigned for the fragments or substituents which are equivalent to the previous ones.

An additional table of the input data specifying the structure of this group should be represented as follows (I1(I2)=2):

NN = 4

KO	KE	ISBJ	
1	2	80	J = 2
1	1	2	J = 3
4	3	52	J = 4

2) For the group R = $CH_3(C_2H_5)_2CCH(C_6H_5)N{=}N-$ (I1 or I2 = = 85), an additional table of the input data is expressed as:

6

1	1	2
2	1	26
2	1	2
4	2	3
4	1	2

3) For the group R = $ClCH_2CH_2O^-$ (I1 or I2 = 66):

3			or	4		
1	1	2		1	1	2
2	1	8		2	1	2
				3	1	52

2.4. Let us give an example of a complete set of the input data for the purpose of calculation of the rate constants of the homolysis in compounds $(NO_2)_3C - NO_2$ and

$NCCH_2$- $OCH(CH_3)_2$ with regard to the given bonds. In case of the first compound one can move in the known value of the heat of formation $\Delta H^{\circ}_{OC(NO_2)_4}$ = 24.4 kcal/mole (ref. see in[2]). R_j of the second compound may be in principle represented either by R_j=$(CH_3)_2CHO$— immediately so far as it is present in Table 1 (I2 = 61), or as a special case of XO-(I2= =66). However, one can see from Table 1 that calculations for the version with I2=61 are impossible due to the lack of the necessary parameters. The groups $(NO_2)_3C^-$ and $NCCH_2^-$ could be considered only as the substituted methyls since they are not represented in Table 1. The $\Delta H^{\circ}_{NCCH_2OCH(CH_3)_2}$ value is unknown.

Therefore the order including four jobs for the above mentioned two compounds is expressed as follows:

```
    4 (number of jobs)
1)  1   2     80    450    24.4
    2
    1   3     80
2)  1   2     80    450    1000
    2
    1   3     80
3)  1   2     61    900    1000
    2
    1   1     30
4)  2   2     66    900    1000
    2
    1   1     30
    3
    1   1      2
    2   2      2
```

3. Output of Results.

Output of the results record is issued both to the screen of the display and into a separate file* whose name is moved

* This file may also be printed

in during the dialog. If the activation entropy is varied and while R_i (and R_j) are substituted methyls, the alternative calculations in two versions of paramerization are executed. These versions are based on different values of the inductive transmission factor $z^{*}_{C\cdot}$ for the carbon atom of the free-radical center (0.36 and 0.39) and other parameters.

If the heat of formation for a reagent is not entered (DH12 > 999), this value will also be calculated if possible. Results are printed as follows:

Job no. ....

After that the table of the input data, the value of the heat of formation and the energy of interaction according to Eq. (4) for the reagent (if DH12 > 999.) are printed. Further the energy of activation and the logarithm of rate constant according to the isoentropic approximation are presented. The results of either one or two variants of the approximation of independent additive entropy follow. After the print of DH12 and I_{ij} values (if DH12 > 999.) the entropy and energy of activation as well as the logarithm of rate constants at a moved-in temperature are given; at the end the mean value of all two or three log k values is printed.

If the calculations are impossible, the corresponding message is output and a subsequent job will be solved. The results record for the above presented four jobs is given in Table 2.

4. On Problem of Predictive Ability of Program and Reliability of Calculated Estimates of log k and ΔH°_{0}.

A practical predictability of the calculation scheme realized in the program is defined by the number of concrete substituents-radicals which are characterized by the minimum-necessary number of parameters (φ_R, σ^{*}_{R}, ΔH_{RH}, $\Delta H^{\neq}_{R\cdot}$ or $\Delta\Delta H^{\neq}_{R\cdot}$.) There are 79 substituents-radicals totally in

Table 1. However, for a part of them can be calculated only the log k value for a given R_i - R_j combination if the $\Delta H^o_{OR_iR_j}$ value is known. For 40 radicals-substituents are known the values of parameters necessary for calculation of the latter value. The number of the respective pairwise combinations is equal to 820.

Calculation of secondary substitution effects ($X_1X_2X_3C^-$, XO-, XN=N-, and XHg-) leads to a significant increase of predictability. Thus, for example, the total number of the $X_1X_2X_3C^-$ type substituted methyl radicals is equal to n^3, where n is the number of different X taken into account. If all possible pairwise combinations of such substituted methyls at n=40 are considered, the number of compounds (predictability) is approximately 10^9.

At the same time the number of different structural types, comprised on this level of parametrization, is limited enough. Except hydrogen and saturated alkyl substituents the sufficient number of the parameters is also known for the following "simple" groups: vinyl and 1-methyl vinyl, allyl and its 1-methyl, 1,1-dimethyl and 2-methyl derivatives, propargyl, phenyl, benzyl, triphenyl methyl, CN, COOH, halogen atoms, OH, OCH_3, ONO_2, NH_2, $NHCH_3$, $N(CH_3)_2$, NO, NO_2, SH, and SCH_3 (see Table 1).

Reliability of the predicted values of the rate constants for the gas phase homolysis and heats of formation for covalent compounds is determined by the reliability of the corresponding parametrizations presented in communications[1-7]. If the rate constants for the gas phase homolysis calculated by the given program are compared with experimental values, i.e. those calculated according to the Arrhenius parameters listed in Ref. 4, their closeness is determined by deviations of the respective lines from the hypersurfaces of the corresponding regressions. Besides, one can use the new experimental data on the kinetic parameters of the gas phase homolysis[8] which are not used for parametrizing equations for the present version of the program.

The bank of parameters used in this program reflects the results of the statistical treatment of the experimental

data both for the gas phase homolysis and the heats of formation for covalent compounds. Both the former and the latter may be conjugated by significant uncertainties. This is expressed in scattering of parallel data for the same compounds. A decision about the reliability of the log k_{exp} values for the gas phase homolysis can be made also by the examples in Table 3 where the calculated values of log k and $\Delta H^{o}_{OR_iR_j}$ are compared with the experimental ones for 14 different compounds.

One can assume the value of 1.5 kcal/mol as a mean value of the standard deviation for different variants of the statistical treatment of kinetic data on the gas phase homolysis presented in papers[3-7]. This corresponds to values 0.33 and 0.66 at temperatures 1000 and 500 K, respectively, in the logarithmic scale of rate constants for the gas phase homolysis. The general reliability of the log k_{calc} values for the isoentropic model (log A_o = 14.64) was investigated by means of the linear regression analysis in coordinates log k_{calc} and log k_{exp} for three temperatures (T_{min}, T_{max} and T_{mean}) of each pair of the experimental log A and E values. Using the experimental heats of formation of reagents the standard deviation s = 0.84 at the intercept 0.05 ± 0.02, slope 0.99 ± 0.01, and the correlation coefficient 0.9723 for the set of 750 lines referred to 91 reactions. s was decreased to 0.58 for 698 lines and 88 reactions (the intercept 0.04 ± 0.01, the slope 0.99 ± 0.01, and the correlation coefficient 0.9867) after the exclusion of significantly deviating lines according to the Student's criterion on confidence level 0.95. These data characterize the general reliability of the prognosis achieved on the ground of the existing parametrization if NVAR=0 for the isoentropic model using the known experimental values of the formation heats of reagents. If the $\Delta H^{o}_{OR_iR_j}$ values are also estimated (DH12 > 999.) and taking NVAR > 0 for the substituted methyls the general reliability of prediction is not essentially varied.

Comparison of the calculated and experimental values in

Table 3 is carried out at different possible variants of representation of structure for reagents (the NVAR values 0, 1 or 2) and also using either the experimental or calculated values of $\Delta H^{\circ}_{OR_iR_j}$. Two or three different versions both for the log k_{calc} and $\Delta H^{\circ}_{0\ calc}$ values are given out as the results. Those may be considered as independent expert estimates. Respective averaged values may also be assumed as the prognosis.

The values of $\Delta H^{\circ}_{0\ calc}$ and $\Delta H^{\circ}_{0\ exp}$ for the first three compounds (2,3-dimethyl butane, 1-butene and nitro methane) in Table 3 differ insignificantly (up to 0.4 kcal/mol). Independent predictions of the log k_{calc} values are also close to one another. The log k_{calc} values for $(CH_3)_2CH(CH_3)CH - CH_3$ are close to the value -9.32, calculated according to the experimental Arrhenius parameters which were used for the parametrization of the present version of the program. The $\Delta H^{\circ}_{0\ calc}$ estimates for CH_3O-CH_3 differ from the experimental value more significantly and this results also in disagreement of the log k_{calc} and log k_{exp} values. Making use of the known experimental ΔH°_0 value leads to the closeness of these values. This is true also for the homolysis of nitromethane .

Comparison of the calculated and experimental values for CCl_3-Br and CF_3-CF_3 shows that the input of the known experimental heats of formation for the reagents makes worse the accordance between the calculated and experimental log k values. Contradiction of the experimental $\Delta H^{\circ}_{0C_2F_6}$ values reported in literature gives evidence about the unreliability of the experimental ΔH°_0 estimates for these compounds. It may be added that in the course of the treatment of the kinetic data on the homolysis, in case of the estimation of the parameters of the substituted methyls, starting from the experimental values of the reagents (variant II in Table 3), the lines for the CF_3-CF_3 homolysis were excluded as deviating significantly.

The compounds with nos 7-12 in Table 3 are various poly nitro substituted alkanes. In their case, the calculated and

experimental ΔH_0° values also differ appreciably (from 0.7 to 12.6 kcal/mol). Use of the experimental ΔH_0° values for prediction of the homolysis log k values leads to a poor compatibility (except tetranitro methane) between the calculated and experimental values. However, the lines for $CF(NO_2)_2C(NO_2)_2-NO_2$ and $C_2H_5C(NO_2)_2-NO_2$ (for such compounds maximum deviations between $\Delta H_{0\ calc}^\circ$ and $\Delta H_{0\ exp}^\circ$ are observed) were excluded during the parametrization which corresponds to variant II of Table 3. Therefore an excellent accordance between the log k_{calc} and log k_{exp} cannot be expected for these compounds. Fair fitting of the calculated and experimental log k values is observed using the computational estimates of the $\Delta H_{OR_iR_j}^\circ$ values. Consequently, the reliability of the listed experimental ΔH_0° values for the indicated polynitro compounds, is quite doubtful.

The last three compounds in Table 3 consist of the substituted XN=N-, XHg- and XO- radicals. Parametrization of the calculation scheme for these types of radicals, both with respect to log k and ΔH_0° values is based on a remarkably poorer data set. Therefore the accordance between the calculated and experimental values of log k and $\Delta H_{OR_iR_j}^\circ$ may be considered satisfactory . $\Delta H_{0\ calc}^\circ$=3.6 and 3.2 kcal/mol for $(CH_3)_3CN{=}NC(CH_3)_3$ are between the alternative experimental estimates ΔH_0°=2.9 and 4.6kcal/mol. However, the latter estimate may be regarded as a more reliable one because a better compatibility between the log k_{calc} and log k_{exp} is achieved taking $\Delta H_{0(CH_3)_3CN=NC(CH_3)_3}^\circ$ = 4.6 kcal/mol. An analogical situation is observed estimating the values for $(CH_3)_2CHHg\text{-}CH(CH_3)_2$. When the values of $\Delta H_{0\ calc}^\circ$ and $\Delta H_{0\ exp}^\circ$ are close, a more reliable prediction of the log k values should be desired. The values of $\Delta H_{0\ calc}^\circ$= -24.7 kcal/mol and log k_{calc}= = -4.30 (430 K) for CH_3OOCH_3 are out of the range of the reported experimental ΔH_0° (-25.5 and -27.5 kcal/mol) and log k_{exp} (see Table 3) values. At the same time the arithmetic mean of available log k_{exp} estimates is rather close

Table 1

Parameters of Calculation Scheme for Free Radicals R• and Respective Substituents R-

σ^{*} and φ are inductive and φ-constants if the substituent R interacts with a "normal" (not halogen-like) substituent.

σ'^{*} and φ' are the same constants if R interacts with halogen-like substituents

s denotes standard deviations of corresponding values.

N_{ψ} is the normalized number of π-electron systems which are able to resonance with the free-radical center in R•. These values for CN and NO_2 correspond to the isoentropic model.

$\Delta H_{R\bullet}$, $\Delta\Delta H_{R\bullet}$ and $\Delta H^{\neq}_{R\bullet}$ are in kcal/mol, $\Delta S^{\neq}_{R\bullet}$ in entr. un.. Unreliable values of parameters $\Delta H^{\neq}_{R\bullet}$ and $\Delta S^{\neq}_{R\bullet}$ are marked by star in the column of "Notes". The $\Delta H_{R\bullet}$ and $\Delta\Delta H_{R\bullet}$ values correspond to the isoentropic model, $\Delta S^{\neq}_{R\bullet}$ and $\Delta H^{\neq}_{R\bullet}$ belong to the version where the entropy is varied.

No	R	σ^{*}	σ'^{*}	φ	φ'	$\Delta H_{R\bullet}$	$s_{\Delta H_{R\bullet}}$	$\Delta\Delta H_{R\bullet}$	$s_{\Delta\Delta H_{R\bullet}}$	$\Delta S^{\neq}_{R\bullet}$	$s_{\Delta S^{\neq}_{R\bullet}}$	$\Delta H^{\neq}_{R\bullet}$	$s_{\Delta H^{\neq}_{R\bullet}}$	ΔH_{RH}	N_{ψ}	Notes
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	H	0.00	0.00	0.00	0.00	51.6	0.00	51.6	0.00	0	-	51.6	-	0.0	0	
2	$CH_3(CX_1X_2X_3)$	0.00	0.00	3.94	3.94	31.8	0.15	48.0	0.20	3.2	0.2	31.7	0.1	-15.9	0	
3	C_2H_5	0.00	0.00	3.20	3.20	25.2	0.40	41.9	0.50	3.2	0.4	25.9	0.3	-16.3	0	
4	C_3H_7	0.00	0.00	3.20	3.20	20.7	0.70	41.3	3.40	3.2	7.8	22.9	2.8	-19.7	0	

Table 1 continued

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
5	$CH(CH_3)_2$	0.00	0.00	2.67	2.67	17.1	0.30	37.3	0.50	4.6	0.4	20.0	0.3	-19.7	0	
6	$CH(CH_3)C_2H_5$	0.00	0.00	2.87	2.87	14.0	0.50	-	-	4.6	1.3	16.7	0.6	-23.6	0	
7	$C(CH_3)_3$	0.00	0.00	2.36	2.36	10.3	0.30	35.9	0.50	7.5	0.3	14.2	0.3	-25.2	0	
8.	CH_2Cl	1.05	0.00	2.94	3.94	28.3	-	45.9	-	-2.0	-	22.7	-	-18.7	0	*
9	CH_2Br	1.01	0.00	3.04	3.94	45.9	-	48.9	-	-3.4	-	38.9	-	-4.8	0	*
10	$CHCl_2$	1.94	0.00	2.43	3.94	18.5	-	37.8	-	-1.8	-	13.8	-	-20.5	0	*
11	$CHBr_2$	1.92	0.00	2.53	3.94	-	-	41.5	-	-3.9	-	39.2	4.2	6.1	0	*
12	CF_3	2.60	0.00	2.09	3.94	-122.7	0.50	50.0	-	5.0	5.7	-121.9	2.6	-165.6	0	*
13	CCl_3	2.65	0.00	2.16	3.94	15.3	1.00	35.7	0.30	-1.6	-	11.2	0.4	-23.3	0	*
14	CBr_3	2.81	0.00	2.24	3.94	52.2	1.00	34.6	-	-4.3	-	46.3	0.7	16.2	0	*
15	$CH=CH_2$	0.60	0.60	3.56	3.56	55.5	0.80	45.0	1.00	11.1	6.2	65.5	0.6	10.5	1	*
16	$C(CH_3)=CH_2$	0.60	0.60	2.91	2.91	40.5	-	34.9	-	15.6	-	56.5	-	8.5	1	*
17	$CH_2CH=CH_2$	0.24	0.24	3.23	3.23	40.9	0.50	32.0	0.50	-0.9	0.5	37.4	0.4	8.6	0	
18	$CH_2C(CH_3)=CH_2$	0.24	0.24	3.40	3.40	31.8	-	-	-	-2.4	-	23.4	-	4.1	0	*
19	$CH(CH_3)CH=CH_2$	0.24	0.24	2.71	2.71	33.1	-	-	-	5.9	-	35.0	-	5.6	0	*
20	$C(CH_3)_2CH=CH_2$	0.24	0.24	2.39	2.39	25.3	-	-	-	9.7	-	29.7	-	-0.4	0	*
21	$CH_2C_6H_5$	0.24	0.24	3.31	3.31	51.8	0.40	34.6	0.50	1.9	0.4	50.1	0.3	17.5	0	
22	$CH_2(1\text{-}C_{10}H_7)$	0.30	0.30	3.30	3.30	65.5	-	-	-	-4.8	-	54.7	-	-	0	*

Table 1 continued

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
23	$CH_2(2\text{-}C_{10}H_7)$	0.30	0.30	3.30	3.30	65.4	-	-	-	-4.8	-	54.6	-	-	0	*
24	$CH_2(2\text{-}C_5H_4N)$	0.35	0.35	3.30	3.30	61.9	-	-	-	-4.4	-	50.8	-	-	0	*
25	$CH_2(3\text{-}C_5H_4N)$	0.30	0.30	3.30	3.30	64.6	-	-	-	-4.4	-	53.5	-	-	0	*
26	C_6H_5	0.60	0.60	3.14	3.14	73.4	0.60	52.4	0.80	2.9	9.1	73.2	0.8	21.0	1	*
27	$1\text{-}C_{10}H_7$	-	-	-	-	74.1	-	-	-	-2.5	-	68.1	-	-	1	*
28	$3\text{-}NO_2C_6H_4$	-	-	-	-	71.7	0.80	-	-	-7.6	-	64.6	1.6	-	1	*
29	$4\text{-}CH_3C_6H_4$	-	-	-	-	62.2	0.60	-	-	-2.2	10.0	56.5	2.5	-	1	*
30	CN	3.50	3.50	5.56	5.56	-	-	-	-	-	-	-	-	16.7	0.75	
31	CF_2NF_2	-	-	-	-	-63.0	-	-	-	4.6	-	-61.9	-	-	0	*
32	$CF(NF_2)_2$	-	-	-	-	-6.9	-	-	-	7.3	-	-4.6	-	-	0	*
33	$C(NF_2)_3$	-	-	-	-	36.4	-	-	-	5.6	-	37.3	-	-	0	*
34	$COCH_3$	1.70	1.70	4.25	4.25	-5.9	0.35	43.3	0.20	1.7	3.4	-8.8	3.4	-	0	*
35	COOH	1.69	1.69	4.10	4.10	-58.7	-	41.2	1.40	-	-	-	-	-99.9	0	
36	CH_2CN	1.33	1.33	2.83	2.83	58.7	0.60	38.5	0.30	-1.7	0.4	53.6	1.1	22.7	0	*
37	$CH_2C{\equiv}CH$	0.60	0.60	3.19	3.19	82.0	-	36.0	-	-	-	-	-	46.1	0	
38	$C(C_6H_5)_3$	0.70	0.70	2.57	2.57	102.0	-	23.4	-	12.4	-	108.0	-	78.6	0	*
39-50	Free positions															
51	F	3.10	3.10	5.45	5.45	18.5	0.50	83.2	0.5	0	-	18.5	-	-64.7	0	
52	Cl	2.70	2.70	4.98	4.98	27.4	1.20	49.4	1.00	0	-	24.4	1.0	-22.0	0	
53	Br	2.60	2.60	4.52	4.52	30.0	0.70	36.7	0.70	0	-	27.8	0.6	-6.8	0	
54	I	2.40	2.40	4.02	4.02	29.3	0.50	22.5	0.60	0	-	26.3	0.4	6.8	0	

Table 1 continued

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
55	OH	1.31	1.31	6.57	6.57	10.5	0.80	74.0	-	-14.5	-	-1.9	-	-61.8	0	*
56	OF	-	-	-	-	28.2	0.80	53.6	-	4.8	1.4	28.3	0.1	-25.4	0	
57	ONO_2	3.76	3.76	7.89	7.89	20.9	0.80	70.0	-	-3.3	3.2	18.3	0.3	-40.0	0	*
58	OCH_3	1.67	1.67	6.57	6.57	4.2	0.30	51.5	1.00	2.9	0.3	3.6	0.2	-45.3	0	
59	OC_2H_5	1.67	1.67	6.57	6.57	-2.2	0.20	50.0	-	-1.6	0.2	-4.5	0.2	-52.0	0	
60	OC_3H_7	1.67	1.67	6.57	6.57	-7.9	0.30	-	-	0.8	0.3	-8.5	0.1	-	0	
61	$OCH(CH_2)_2$	1.67	1.67	-	-	-	-	-	-	-	-	-	-	-	0	
62	$OC(CH_3)_3$	1.67	1.67	-	-	-15.9	0.15	-	-	5.8	0.4	-15.1	0.1	-	0	
63	$OCH=CH_2$	2.40	2.40	-	-	12.6	-	-	-	7.5	-	14.3	-	-	0	*
64	OC_6H_5	2.40	2.40	-	-	17.1	-	-	-	-2.9	-	15.6	4.5	-	0	*
65	OCF_3	-	-	-	-	-	-	-	-	-	-	-	-	-	0	
66	OX	-	-	8.22	8.22	-6.3	-	55.5	-	-	-	-	-	-	0	
67-70	Free positions															
71	NH_2	0.72	0.72	5.88	5.88	44.9	0.30	53.1	0.90	-3.2	0.3	37.1	0.3	-9.3	0	
72	NF_2	-	-	-	-	8.6	0.40	-	-	3.9	1.0	8.7	0.2	-	0	
73	$NHCH_3$	1.00	1.00	5.88	5.88	39.2	-	-	-	1.3	-	40.9	-	-2.0	0	*
74	$N(CH_3)_2$	1.10	1.10	5.88	5.88	35.9	-	35.3	-	1.2	-	37.1	-	0.6	0	*
75	NHC_6H_5	-	-	-	-	60.8	0.80	34.5	-	-4.7	0.2	55.0	1.5	26.3	0	
76	$N(CH_3)C_6H_5$	-	-	-	-	63.1	1.90	25.7	-	-8.3	-	53.1	1.9	37.4	0	*
77-78	Free positions															
79	NO	-	-	-	-	21.2	0.40	-	-	3.8	1.0	20.5	0.3	-	-	

Table 1 continued

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
80	NO_2	3.55	3.55	6.10	6.10	7.4	0.25	29.3	0.50	3.6	0.3	7.3	0.2	-22.7	0.355	
81	SH	1.52	1.52	4.21	4.21	18.7	0.70	38.2	0.90	-3.8	0.6	13.6	0.5	-19.5	0	
82	SCH_3	1.44	1.44	4.21	4.21	14.7	-	35.1	1.40	-2.8	-	10.3	-	-18.4	0	*
83	SC_6H_5	-	-	-	-	42.8	-	-	-	0.3	-	40.5	-	-	0	*
84	SO_2CH_3	-	-	-	-	-74.5	0.80	-	-	1.3	2.5	-74.3	1.1	-	0	*
85	N=NX	-	-	4.58	-	-	-	36.1	-	-	-	-	-	-	0	
86-100	Free positions															
101	$Si(CH_3)_3$	-	-	-	-	-1.2	0.40	-	-	-1.9	2.3	-5.4	0.2	-	0	*
102	$ZnCH_3$	-	-	-	-	48.9	-	-	-	-16.0	-	30.8	-	-	0	*
103	$CdCH_3$	-	-	-	-	53.8	0.65	-	-	-11.7	1.3	41.7	0.6	-	0	*
104	HgR	-	-	-	-	-	-	-	-	-	-	-	-	-	0	
105	HgCl	-	-	-	-	22.7	1.00	-	-	-6.3	-	13.3	2.0	-	0	*
106	HgBr	-	-	-	-	29.1	-	-	-	-0.4	-	25.9	-	-	0	*
107	$HgCH_3$	-	-	-	-	51.1	0.40	-	-	-1.5	4.2	47.5	0.7	-	0	*
108	HgC_2H_5	-	-	-	-	47.8	0.90	-	-	-1.9	4.9	41.3	2.7	-	0	*
109	$HgCH(CH_3)_2$	-	-	-	-	35.4	0.80	-	-	-16.6	-	25.0	0.7	-	0	*
110	$SnCl_2CH_3$	-	-	-	-	-8.2	-	-	-	-5.4	-	-15.6	-	-	0	*
111	$Sn(CH_3)_3$	-	-	-	-	33.9	0.80	-	-	3.2	-	30.2	4.7	-	0	
112	$Pb(C_2H_5)_3$	-	-	-	-	57.6	0.90	-	-	-11.2	2.7	48.8	0.8	-	0	
113-150	Free positions															

Table 2

Example of Results Record Print

```
JOB NO.   1
----------
NVAR I1  I2    T K     DH12
  1   2  80  450.00    24.40

NN=  2
 1  3 80

APPROXIMATION OF UNIVERSAL PREEXPONENTIAL FACTOR

ENERGY(ENTHALPY) OF ACTIVATION =    36.34 KCAL/MOL
LOG K ( 450. K) =    -3.01  1/SEC

APPROXIMATION OF INDEPENDENT ADDITIVE ENTROPY OF  ACTIVATION

ENTROPY OF ACTIVATION=     9.65 ENTR. UN.
ENERGY(ENTHALPY) OF ACTIVATION =    35.27 KCAL/MOL
LOG K ( 450. K) =    -2.04  1/SEC

APPROXIMATION OF INDEPENDENT ADDITIVE ENTROPY OF  ACTIVATION

ENTROPY OF ACTIVATION=    10.37 ENTR. UN.
ENERGY(ENTHALPY) OF ACTIVATION =    37.15 KCAL/MOL
LOG K ( 450. K) =    -2.80  1/SEC

MEAN LOG K ( 450. K) =    -2.62  1/SEC


JOB NO.   2
----------
NVAR I1  I2    T K     DH12
  1   2  80  450.00 1000.00

NN=  2
 1  3 80

HEAT OF FORMATION OF THE REAGENT =    25.05 KCAL/MOL
ENERGY OF INTERACTION =    45.00 KCAL/MOL
APPROXIMATION OF UNIVERSAL PREEXPONENTIAL FACTOR

ENERGY(ENTHALPY) OF ACTIVATION =    35.24 KCAL/MOL
LOG K ( 450. K) =    -2.47  1/SEC

HEAT OF FORMATION OF THE REAGENT =    25.09 KCAL/MOL
ENERGY OF INTERACTION =    45.02 KCAL/MOL
APPROXIMATION OF INDEPENDENT ADDITIVE ENTROPY OF  ACTIVATION

ENTROPY OF ACTIVATION=     9.65 ENTR. UN.
ENERGY(ENTHALPY) OF ACTIVATION =    34.57 KCAL/MOL
LOG K ( 450. K) =    -1.71  1/SEC
```

```
HEAT OF FORMATION OF THE REAGENT =   25.09 KCAL/MOL
ENERGY OF INTERACTION =   45.02 KCAL/MOL
APPROXIMATION OF INDEPENDENT ADDITIVE ENTROPY OF  ACTIVATION

ENTROPY OF ACTIVATION=   10.37 ENTR. UN.
ENERGY(ENTHALPY) OF ACTIVATION =   36.46 KCAL/MOL
LOG K ( 450. K) =   -2.47  1/SEC

MEAN LOG K ( 450. K) =   -2.22  1/SEC


JOB NO.   3
----------
NVAR I1  I2    T K    DH12
  1   2  61  900.00 1000.00

NN=  2
 1  1 30

SORRY ,CALCULATIONS ARE IMPOSSIBLE DUE TO THE LACK OF
PARAMETERS


JOB NO.   4
----------
NVAR I1  I2    T K    DH12
  2   2  66  900.00 1000.00

NN=  2
 1  1 30

NN=  3
 1  1  2
 2  2  2

HEAT OF FORMATION OF THE REAGENT =  -17.68 KCAL/MOL
ENERGY OF INTERACTION =   23.59 KCAL/MOL
APPROXIMATION OF UNIVERSAL PREEXPONENTIAL FACTOR

ENERGY(ENTHALPY) OF ACTIVATION =   69.97 KCAL/MOL
LOG K ( 900. K) =   -2.35  1/SEC


APPROXIMATION OF INDEPENDENT ADDITIVE ENTROPY OF  ACTIVATION

SORRY, CALCULATIONS ARE IMPOSSIBLE DUE TO THE LACK OF
PARAMETERS
```

Table 3.

Comparison of Calculated and Experimental log k (Taking into Account Statistical Factor) and $\Delta H^{\circ}_{OR_iR_j}$ Values

I corresponds to the isoentropic model, II and III for the two above mentioned variants of substituted methyls if the activation entropy is varied.

No	Compound	NVAR	T K	log k_{calc}				log k_{exp}		ΔH°_0 calc		ΔH°_0 exp
				I	II	III	Mean		Mean	I	II and III	
1	2	3	4	5	6	7	8	9	10	11	12	13
1.	$(CH_3)_2CH(CH_3)CH-CH_3$	1	700	-8.92	-9.09	-9.04	-9.02	-9.32[4]; -6.95[a]	-8.14	-32.3	-32.3	-32.7[4]
		1	700[a]	-8.83	-9.20	-9.15	-9.06	"	"	-	-	-32.7
2.	$CH_2=CHCH_2-CH_3$	1	800	-4.19	-3.68	-4.11	-3.99	-3.43[4]; -5.08[4]; -3.99[4]; -3.23[4]; -4.18[8]	-3.98	5.4	5.4	5.0[4]
		0	800	-3.81	-3.66	-	-3.73	"	"	5.5	5.5	"
		1	800[a]	-4.15	-3.81	-4.23	-4.06	"	"	-	-	5.0
		0	800[a]	-3.85	-3.79	-	-3.83	"	"	-	-	5.0

Table 3 continued

1	2	3	4	5	6	7	8	9	10	11	12	13
3.	$CH_3 - NO_2$	0	700	-1.99	-2.07	-	-2.03	-1.96[4]; -2.13[4]; -2.18[4]; -1.63[4]; -3.13[4]; -2.60[4]; -2.01[4]; -2.97[8]	-2.33	-14.57	-14.57	-14.55[4]
		0	700[a]	-2.12	-2.07	-	-2.09	"	"	-	-	14.55
4.	CH_3O-CH_3	1	800	-6.56	-	-	-6.56	-6.06[4]; -4.93[4]; -5.90[8]; -6.47[8]; -6.56[8]; -6.20[8]; -6.29[8]; -6.24[8];	-6.08	-41.8	-	-40.1[4]
		0	800	-5.47	-4.73	-	-5.10	"	"	-35.3	-35.3	"
		1	800[a]	-5.99	-	-	-5.99	"	"	-		-40.1
		0	800[a]	-6.13	-6.04	-6.04	-6.07	"	"	-	-	-40.1
5.	CCl_3-Br	1	800	-0.75	-0.59	0.15	-0.40	-0.36[4]	-0.36	-12.0	-12.0	-8.8[4]; -8.2[4]
		0	800	-0.27	-1.14	-	-0.71	"	"	-12.3	-12.3	"
		1	800[a]	0.19	0.30	1.03	0.50	"	"	-	-	-8.8
		0	800[a]	-0.14	-0.18	-	-0.16	"	"	-	-	-8.8
		1	800[a]	0.35	0.46	1.19	0.67	"	"	-	-	-8.2
		0	800[a]	0.03	-0.02	-	0.00	"	"	-	-	-8.2

Table 3 continued

1	2	3	4	5	6	7	8	9	10	11	12	13
6.	$CF_3 - CF_3$	1	1500	1.34	1.23	2.09	1.55	3.88[4]; 4.47[4]	4.18	-307.9	-312.3	-320.1[4];-306[2]
		0	1500	2.87	4.93	-	3.90	"	"	-312.0	-317.6	"
		1	1500[a]	-0.35	0.72	1.74	0.70	"	"	-	-	-320.1
		0	1500[a]	3.76	4.56	-	4.16	"	"	-	-	-320.1
		1	1500[a]	1.71	2.78	3.80	2.76	"	"	-	-	-306.0
		0	1500[a]	5.81	6.62	-	6.21	"	"	-	-	-306.0
7.	$C(NO_2)_3-NO_2$	1	450	-2.47	-1.71	-2.47	-2.22	-2.93[4];-3.05[4]; -2.93[8]	-2.97	25.1	25.1	24.4[4]
		1	450[a]	-3.01	-2.04	-2.80	-2.62	"	"	-	-	"
8.	$C(NO_2)_3C(NO_2)_2-NO_2$	1	400	-3.92	-2.46	-3.38	-3.25	-3.04[4]	-3.04	47.7	47.8	46.0[4](45.6[2]); 54.6[2]
		1	400[a]	-5.10	-3.42	-4.34	-4.29	"	"	-	-	46.0
		1	400[a]	-0.40	1.27	0.36	0.41	"	"	-	-	54.6
9.	$CF(NO_2)_2C(NO_2)_2-NO_2$	1	400	-4.03	-2.81	-3.70	-3.51	-3.12[4]	-3.12	-0.1	-6.3	-12.7[4]
		1	400[a]	-11.18	-6.30	-7.18	-8.22	"	"	-	-	-12.7
10.	$C_2H_5C(NO_2)_2-NO_2$	1	450	-4.24	-3.70	-4.21	-4.05	-4.16[4]	-4.16	-7.0	-6.9	-10.6[4]
		1	450[a]	-6.23	-5.47	-5.99	-5.90	"	"	-	-	-10.6

Table 3 continued

1	2	3	4	5	6	7	8	9	10	11	12	13
11.	$C_3H_7CH(NO_2)-NO_2$	1	500	-3.98	-3.27	-3.97	-3.74	-4.37[4]	-4.37	-22.4	-22.4	-25.9[4]
		1	500[a]	-5.71	-4.81	-5.52	-5.35	"	"	-	-	-25.9
12.	$(CH_3)_3CN=N-C(CH_3)_3$	2	550	-1.65	-	-	-1.65	-0.97[4]; -0.24[4]; -1.01[8]; -0.91[8]	-0.78	3.6	-	2.9[4]; 4.6[4]
		1	550	-1.82	-	-	-1.82	"	"	3.2	-	"
		2	550[a]	-1.79	-	-	-1.79	"	"	-	-	2.9
		1	550[a]	-1.76	-	-	-1.76	"	"	-	-	2.9
		2	550[a]	-1.11	-	-	-1.11	"	"	-	-	4.6
		1	550[a]	-1.09	-	-	-1.09	"	"	-	-	4.6
13.	$(CH_3)_2CHHg-CH(CH_3)_2$	2	500	-0.52	-	-	-0.52	-1.10[4]; -1.76[8]; -1.69[8]	-1.52	19.0	-	19.0[4]; 20.0[4]
		1	500	-0.47	-	-	-0.47	"	"	19.1	-	"
		2	500[a]	-0.39	-	-	-0.39	"	"	-	-	19.0
		1	500[a]	-0.29	-	-	-0.29	"	"	-	-	19.0
		0	500[a]	0.00	-0.97	-	-0.48	"	"	-	-	19.0
		2	500[a]	0.05	-	-	0.05	"	"	-	-	20.0
		1	500[a]	0.15	-	-	0.15	"	"	-	-	20.0
		0	500[a]	0.44	-0.53	-	-0.05	"	"	-	-	20.0

Table 3 continued

1	2	3	4	5	6	7	8	9	10	11	12	13
14.	$CH_3O - OCH_3$	2	430	-1.56	-	-	-1.56	-3.14[4]; -2.74[4]; -3.30[8]; -3.15[8]	-3.08	-24.7	-	-25.5[4]; -27.5[4]
		0	430[a]	-2.54	-2.40	-	-2.47	"	"	-	-	-	-25.5
		0	430[a]	-3.55	-3.42	-	-3.48	"	"	-	-	-	-27.5

[a] The log k_{calc} values for these jobs are calculated using the $\Delta H^{\circ}_{OR_iR_j}$ values listed in the last column.

to the mean value of the log k_{calc} estimates calculated using the alternative $\Delta H^{o}_{0\ exp}$ values for CH_3OOCH_3.

It must be emphasized in conclusion that the present version of parametrization is not final yet. Improved predictive ability and more reliable estimated values both of the rate constant logarithms for the gas phase homolysis, and the heats of formation for covalent compounds may be realized proceeding from the reparametrization initiated in paper[8]. At that, recent more reliable data both on the gas phase kinetics[8] and the heats of formation will be used.

As for the program described in this communication, it does not certainly depend on concrete parameter values but reflects only the structure of the calculation scheme used. A possible improvement of the latter causes some changes in the algorithm, which is realized in the present program, as well as the changes for this program.

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REACTIVITY OF DERIVATIVES OF PHENYLANTHRANILIC ACID. I.REACTION KINETICS OF ALKALINE HYDROLYSIS OF 4^1-DERIVATIVES OF ß-DIMETHYL-AMINOETHYL ETHER OF 4-CHLORO-N-PHENYL-ANTHRANILIC ACID IN BINARY DIOXANE-WATER SOLVENT

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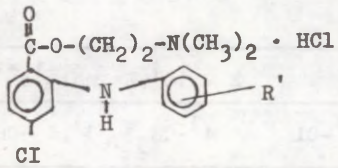
Kinetics of alkaline hydrolysis of five derivatives of ß-dimethyl amino ethyl ether of 4-chloro-N-phenyl-anthranilic acid has been studied in the binary dioxane-water solvent, the temperature range being 298-358 K. Bimolecular reaction rate constants were also determined. The thermodynamic activation parameters found indicate that there is an isokinetic correlation with the enthalpic control type within the limits of a reaction series. Kinetic data obey the equations of Arrhenius and Hammett. The method of multiple regression analysis has been applied in order to suggest the two-parameter correlation equation with a cross term and determine the isoparametric values of the correlated parameters (δ and T).

The ethers of aromatic acids, especially those of phenyl-anthranilic acid have a wide range of biological effect

and are thoroughly studied in order to find the compounds having antiinflammatory, antipyretic, analgetic and other properties[1,2,3]. Therefore it was interesting to study the reactivity of 4-derivatives of ß-dimethyl aminoethyl ether of 4-chloro-N-phenyl-athranilic acid obtained by us. We applied the reaction of alkaline hydrolysis (as a pattern) since it is one possible variant of metabolism of these compounds in biological media.

Table 1

Derivatives of ß-Dimethyl amino Ethyl Ether of 4-Chloro-N-Phenyl-anthranilic Acid



R^1	Meeting point	Found % N	Brutto formula	Calculated %, N	R_f
H	173-174	7.9	$C_{17}H_{20}Cl_2N_2O_2$	7.7	0.60
4^1-Cl	130-131	7.4	$C_{17}H_{19}Cl_3N_2O_2$	7.1	0.66
4^1-CH_3	86-86	7.7	$C_{18}H_{22}Cl_2N_2O_2$	7.5	0.62
3^1, 4-CH_3	120-121	7.5	$C_{19}H_{24}Cl_2N_2O_2$	7.3	0.64
4^1-OCH_3	141-142	7.5	$C_{18}H_{22}Cl_2N_2O_2$	7.2	0.63

The constants of reaction rate were calculated according to the change in the concentration of sodium hydroxide, determined by potentiometric titration in time. The methods of kinetic measurements will be described further. The process can be described by a kinetic second order equation, since the values of reaction rate constants (Table 2) at different time moments, calculated according to Eq. (1) are quite stable.

$$k = \frac{1}{ßt(b-a)} \cdot \ln \frac{a(b-x)}{b(a-x)} \qquad (1)$$

a,b denote the initial concentrations of ether and alkali, respectively, in mol/l;

x is the quantity of the compound which underwent the reaction at time t(s);

ß is the correction factor taking into consideration the concentration change of the reagents in case of the thermal expansion of the solvent from 293 K to the experiment temperature.

Table 2

Rate Constants of the Reaction of Alkaline Hydrolysis of Derivatives of ß-Dimethylaminoethyl. Ether of 4-Chloro-N-Phenyl-anthranilic Acid in the Dioxane-Water Mixture at Various Temperatures

R^1		$k \cdot 10^4$, L· $mol^{-1}s^{-1}$			
T,K	H	4^1-Cl	4^1-CH_3	$3^1,4^1$-CH_3	4^1-OCH_3
298	2.35±0.06	6.90±0.02	1.43±0.06	1.17±0.04	1.08±0.06
308	3.66±0.03	10.3 ±0.09	2.30±0.05	1.91±0.04	1.76±0.04
318	6.05±0.07	15.7 ±0.14	3.90±0.08	3.27±0.07	3.03±0.07
328	10.3±0.07	25.5±0.11	6.87±0.11	5.80±0.09	5.41±0.06
338	16.9±0.12	39.4±0.16	11.6±0.14	9.79±0.16	9.16±0.09
348	26.4±0.11	58.5±0.21	18.3±0.23	15.8±0.18	14.7±0.10
358	40.6±0.24	85.4±0.18	28.8±0.18	15.0±0.27	23.6±0.09

The constants of rate of the studied reaction series depend on the substituents' nature and position in the non-anthranilic molecule fragment at all temperatures applied (Table 2). The electron-donor substituents make the reaction rate drop, while the electron-acceptor ones accelerate the reaction proportinally to the Hammett σ- constant[4].

The polyterms of the rate constant logarithms have a linear character. It is confirmed by the high values of the correlation coefficient of the Arrhenius equation (Table 3).

Table 3

Parameters of the Arrhenius Equation of Reaction of Alkaline Hydrolysis of Derivatives of ß-Dimethylaminoethyl Ether of 4-Chloro-N-Phenyl-anthranilic Acid

$$\log k = \log k_o + a_1 \cdot 10^3/T \qquad (2)$$

R^1	$+a_1$	$\log k_o$	r	S
H_1	-2.236±0.048	3.84±0.12	0.9989	0.0189
4^1-Cl	-1.974±0.031	3.43±0.21	0.9988	0.0175
4^1-CH_3	-2.354±0.062	4.02±0.17	0.9981	0.0184
$3^1,4^1$-CH_3	-2.399±0.027	4.08±0.31	0.9999	0.0182
4^1-OCH_3	-2.402±0.034	4.07±0.27	0.9914	0.0150

It enabled us to find the activation energy E_A and the pre-exponential factor A according to the Arrhenius equation (Table 4).

Table 4

Kinetic Parameters of Activation (E_A and ln A) of Reaction of Alkaline Hydrolysis of Derivatives of ß-Dimethylaminoethyl Ether of 4-Chloro-N-Phenyl-anthranilic Acid

R^1	E_A kcal/mol	ln A	r	S
H	10.24±0.16	8.86±0.39	0.9990	0.0041
4^1-Cl	9.04±0.15	7.91±0.36	0.9989	0.0040
4^1-CH_3	10.83±0.23	9.35±0.57	0.9980	0.0064
$3^1,4^1$-CH_3	10.98±0.15	9.42±0.38	0.9916	0.0042
4^1-OCH_3	11.06±0.16	9.46±0.39	0.9912	0.0044

The thermodynamic parameters of activation (enthalpy $\Delta H^{\neq}$, entropy $\Delta S^{\neq}$, free energy $\Delta G^{\neq}$) were determined ac-

cording to the Eyring equation[5] (Table 5).

Table 5.

Thermodynamic Parameters of Activation of the Reaction of Alkaline Hydrolysis of Derivatives of ß-Dimethylaminoethyl Ether of 4-Chloro-N-Phenyl-anthranilic Acid

R^1	$H^{\neq}$ kcal/mol	$S^{\neq}$ e.u.	r	S	$G^{\neq}_{298}$ kcal/mol
H	9.58±0.15	43.1±0.4	0.9989	0.0042	22.4
4^1-CI	8.39±0.14	45.0±0.3	0.9988	0.0040	21.8
4^1-CH_3	10.19±0.23	42.1±0.6	0.9979	0.0063	22.7
$3^1,4^1$-CH_3	10.34±0.15	42.0±0.4	0.9910	0.0041	22.9
4^1-OCH_3	10.41±0.15	41.9±0.4	0.9908	0.0042	22.9

The quantitative estimation of the substituents' effect on the reactivity of the ethers of 4-chloro-N-phenyl-anthranilic acid was made according to the Hammett equation (Table 6).

Table 6

Parameters of the Hammett Equation for the Reaction of Alkaline Hydrolysis of Derivatives of ß-Dimethylaminoethyl Ether of 4-Chloro-N-Phenyl-anthranilic Acid

$$\log k = \log k_o + a_2\sigma \qquad (3)$$

T,K	$a_2=\rho$	$\log k_o$	r	S
298	1.276±0.089	-3.632±0.008	0.9986	0.0052
308	1.202±0.009	-3.433±0.008	0.9969	0.0017
318	1.119±0.059	-3.218±0.052	0.9991	0.0044
328	1.055±0.012	-2.985±0.056	0.9932	0.0031
338	0.9924±0.0072	-2.772±0.006	0.9968	0.0019
348	0.9404±0.0065	-2.578±0.058	0.9946	0.0044
358	0.8756±0.0170	-2.392±0.015	0.9988	0.0050

ϱ has a positive value, being thus in agreement with the literature data[6] on the nucleophilic reaction mechanism of the alkaline hydrolysis. The value is rather small evidently either owing to the isolating influence of the bridge imino-group[7], or the remoteness of the substituence from the reaction center. With the rising of temperature ϱ decreases, i.e. the reaction's susceptibility to the substituent effect becomes weaker.

The quantitative estimation of the mutually perturbing effect of the both parameters (σ constant of substituents and T) was given according to the equation with one cross term[6]:

$$f(x_1,x_2) = f_o + a_1x_1 + a_2x_2 + a_{12}x_1x_2 \qquad (4)$$

where f_o, a_1, a_2, a_{12} are the constants characterizing the susceptibility of the reaction series to the effect of the interacting parameters.

In order to find the constants of Eq. (4), multiple regression analysis with application of the algorithm given in[8] was used. The statistical reliability of the obtained results was determined by the F-criterion of Fischer. Calculations were conducted on a EC-1045 computer. The values of the constants are given in Table 7.

Table 7.

Values of Susceptibility Parameters of Eq. (4) and Isoparametric Values (IPV) of Correlation Parameters

Equation parameters	Variable or cross term	Susceptibility factor	Numerical value of susceptibility factor	IPV
f_o	$\log k_o$	-	3.837 ± 0.015	β =653
X_1	σ	a_1	-1.063 ± 0.042	X_1=+3.22
X_2	$1/T\cdot10^3$	a_2	-2.234 ± 0.031	X_2= 1.53
X_1X_2	$\sigma\cdot 1/T\cdot10^3$	a_{12}	0.694 ± 0.012	

IPV were calculated using the data of Table 6 according to the known formulas:

$$x_1 = -a_2/a_{12} \quad x_2 = -a_1/a_{12} \quad \beta = -a_{12}/a_1 \cdot 10^3 \qquad (5)$$

The data of Table 7 show that in the studied reaction series holds the isokinetic correlation. It is worth mentioning that the value β of isokinetic temperature calculated according to Eq. (5) practically coincides with those of β, found independently according to Eq. 7 (Table 8):

$$\log k_{T_2} = \text{const} + \alpha \log k_{T_1} \qquad (6)$$

Table 8

Determining of Isokinetic Temperature of the Reaction of Alkaline Hydrolysis of Derivatives of β-Dimethyl-Aminoethyl Ether of 4-Chloro-N-Phenyl-anthranilic Acid

Temperature, K		α	r	S	β, K
T_1	T_2				
298	318	0.886	0.9976	0.0078	662
298	338	0.785	0.9953	0.0110	663
298	358	0.693	0.9982	0.0077	655
318	338	0.887	0.9991	0.0077	664
318	358	0.782	0.9918	0.0079	653
338	358	0.883	0.9924	0.0063	647

β = 657

The existence of isokinetic correlation in case of the studied reaction series can also be confirmed by the linear correlation between the $\Delta H^{\neq}$ - log k_T, $\Delta H^{\neq}$ - $\Delta S^{\neq}$, E_A - log A, ϱ - 1/T (Table 9), shown by the linear regression analysis. Reliability of the calculated correlation parameters for all equations was checked by means of the Student's t-test[8]. It was proved that all the parameters were statistically significant, their reliability exceeding 95%.

The isokinetic temperature β exceeds the experimental temperature range, thus referring to the possible enthalpic control for the alkaline hydrolysis reaction of the derivatives of β-dimethylaminoethyl ether of 4-chloro-N-phenyl-anthranilic acid.

Table 9

Determining of Isokinetic Temperature. Correlation Parameters of $y = a + bx$.
Equations of Dependences of Kinetic and Activation Parameters of Alkaline Hydrolysis
Reaction of ß-Dimethylaminoethyl Ether of 4-Chloro-N-Phenyl-anthranilic Acid

X	Y	a	B	r	s	ß,K
$\log k_{298}$	$\Delta H^{\neq}$	$(0.373 \pm 0.018) \cdot 10^3$	$(-2.54 \pm 0.02) \cdot 10^3$	0.9992	0.030	645
$\log k_{308}$	$\Delta H^{\neq}$	$(0.419 \pm 0.018) \cdot 10^3$	$(-2.67 \pm 0.02) \cdot 10^3$	0.9922	0.030	652
$\log k_{318}$	$\Delta H^{\neq}$	$(0.352 \pm 0.019) \cdot 10^3$	$(-2.87 \pm 0.03) \cdot 10^3$	0.9919	0.032	645
$\log k_{328}$	$\Delta H^{\neq}$	$(0.506 \pm 0.020) \cdot 10^3$	$(-3.04 \pm 0.05) \cdot 10^3$	0.9909	0.031	647
$\log k_{338}$	$\Delta H^{\neq}$	$(0.625 \pm 0.024) \cdot 10^3$	$(-3.23 \pm 0.04) \cdot 10^3$	0.9936	0.033	648
$\log k_{348}$	$\Delta H^{\neq}$	$(0.754 \pm 0.014) \cdot 10^3$	$(-3.43 \pm 0.05) \cdot 10^3$	0.9928	0.035	650
$\log k_{358}$	$\Delta H^{\neq}$	$(0.820 \pm 0.017) \cdot 10^3$	$(-3.67 \pm 0.02) \cdot 10^3$	0.9943	0.026	647
$\Delta S^{\neq}$	$\Delta H^{\neq}$	$(37.3 \pm 0.6) \cdot 10^3$	643 ± 9	0.9990	0.121	643
log A	E_A	-1.107 ± 0.021	295 ± 10	0.9992	0.290	680
1/T	Q	-1.098 ± 0.056	707 ± 15	0.9951	0.041	644

$\bar{B} = 650$

Experimental

Reactives. Dioxane with a sign "oscillation" was used without additional purification.

ß-dialkylaminoethyl ethers of 4-chloro-N-phenylanthranilic acid were synthesized according to the known methods[9,10]. Their purity was checked according to the thin layer chromatography method (system of propanol-water 1:1).

For preparation of solutions, sodium hydroxide was purified from carbonates according to method[11].

Method of kinetic experiment similar to[12] was used. Solutions of ethers with concentration of 0.04 mol/l were prepared by solving an exactly weighed portion in a 50.00 ml measuring flask in a binary dioxane-water solvent (60% of dioxane). In another flask was the solution of sodium hydroxide in the same binary solvent. The alkali concentration was approximately four times higher than that of ether. The measuring flasks were kept in the thermostat for 20 min (thermostating accuracy being $\pm 0.1^{\circ}C$), after that their contents were poured into a 100.0 ml empty flask. Samples of 10.00 ml were taken at certain time intervals. The reaction was inhibited by sharp cooling of the reaction mixture. The sodium hydroxide concentration in the mixture was determined by means of potentiometric titration on an ionomer EV-74 (titrant 0.05 n; HCl aqueous solution). Each experiment was repeated three times, including 7-8 measurements each (depth of transformation was 70-80 %). The accuracy of the obtained parameters was estimated using the methods of mathematical statistics (with a 0.95 probability)[13]. The thermodynamic activation parameters were calculated according to the known equations applying the method of least squares on a computer "Elektronika B3-34" with standard programs[14].

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STRUCTURAL THEORY OF ELECTROLYTE SOLUTIONS. IV. TEMPERATURE DEPENDENCE OF ACTIVITY COEFFICIENTS OF STRONG ELECTROLYTES IN AQUEOUS SOLUTIONS.

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The results of the statistical verification of the structural theory of electrolyte solutions proposed earlier by the author are presented on the basis of the experimental activity coefficient data at different temperatures.

The temperature dependence of the solvent restructurization parameters, V_s, has been discussed. A linear free energy relationship was observed for these parameters, corresponding to the different electrolytes.

The results of the statistical verification of a simple structural theory of electrolyte solutions[1] were given in the previous publications[2-3]. The experimental data on the activity and osmotic coefficients at standard conditions (1 atm, 298.15 ^{o}K) were used for this purpose.

In the present article this simple theory is used for the description of the temperature dependence of the activity coefficients of strong electrolytes in aqueous solutions. According to the basic postulate of the structural theory, the different interaction types between the solution particles are assumed to be independent. Thus, the partial excess free

energy of an electrolyte in the solution is given by the following equation:

$$\Delta G_{ex} = \Delta G_{el} + \Delta G_{is}, \qquad (1)$$

where ΔG_{el} is the term connected with the electrostatic interionic interaction, and ΔG is the partial excess free energy of the ion-solvent interaction, Proceeding from the modified Poisson-Boltzmann electrostatic model[4], the following formula can be derived for the term ΔG_{el}:

$$\Delta G_{el} = \frac{N_A(\nu_+ + \nu_-)}{2} \frac{z_+ z_- e^2}{\varepsilon \bar{l}} =$$

$$= \frac{24.7689}{\varepsilon} z_+ z_- (\nu_+ + \nu_-) \sqrt[3]{\nu c}, \qquad (2)$$

where N_A is the Avogadro's number, $\nu = \nu_+ + \nu_-$ denotes the number of ions in the electrolyte molecule, ε is the dielectric permittivity of the solvent, c is the molar concentration of the electrolyte in the solution, and $\bar{l}$ denotes the statistically average distance between the nearest-neighboring counterions. If to take into account the formal relationship between the partial excess fee energy and activity coefficients, the corresponding expression for the electrostatic term in the activity coefficient can be obtained:

$$(\ln f_{\pm})_{el} = \frac{24.7689}{\varepsilon RT} z_+ z_- \sqrt[3]{\nu c} = a_t \sqrt[3]{c}, \qquad (3)$$

where R is the universal gas constant and T temperature ($^{\circ}$K). This term is calculable theoretically at the given values of ε and T (a_t is the theoretical multiplier).

The second term in Eq. (1) has a simple form of the concentrational dependence[1]:

$$\Delta G_{is} = 2\nu RTV_s c, \qquad (4)$$

where V_s denotes the specific solvent restructurization volume for a given electrolyte . The parameter V_s is numerically equal to such volume around the 1 mole of electro-

lyte ions, in the case of which the solvent molecules are transferred from the unperturbed state corresponding to the pure solvent, into the fully structurized state. The negative V_s values correspond to the total destruction of the solvent intrinsic structure in this volume. The respective term in the activity coefficient formula is given by the following expression:

$$(\ln f_{\pm})_{is} = 2V_s c = B_i c, \qquad (5),$$

where B_i is now a specific parameter for a given electrolyte in a given solvent.

The statistical treatment of the experimental data proceeded by the linear least-squares method according to the following equation:

$$\ln f_{\pm} - a_t \sqrt[3]{c} = \Delta \ln f_{\pm} + B_i c , \qquad (6)$$

where the left side of this equation is a known function and $\Delta \ln f_{\pm}$ denotes a small intercept due to the different standardization of the experimental activity coefficients given in the literature.

The results of the statistical data treatment are presented in Table 1. The validity of Eq. (6) is confirmed by the excellent statistical fitness parameters (the correlation coefficient $r \geqslant 0.999$ and the standard deviation $s < 0.01$ for most cases) for every individual activity coefficients' set investigated.

The paramount interest is connected with the study of the temperature dependence of the B_i- parameters, which now are the only unknown (empirical) parameters in the description. These parameters determine the numerical value of the partial excess free energy ΔG_{is} :

$$\Delta G_{is} = \nu RTB_i c \qquad (7)$$

This free energy is characterized by the corresponding enthalpy and entropy terms, ΔH_{is} and ΔS_{is}:

$$\Delta G_{is} = \Delta H_{is} - T\Delta S_{is}, \qquad (8)$$

and, consequently

$$B_i = \frac{\partial \Delta G_{is}}{\partial c} \cdot \frac{1}{\nu RT} = \frac{1}{\nu RT}\left(\frac{\partial \Delta H_{is}}{\partial c}\right) - \frac{1}{\nu R}\left(\frac{\partial \Delta S_{is}}{\partial c}\right) =$$

$$= \frac{a_1}{T} + b_1 , \qquad (9)$$

where the derivatives $(\partial H_{is}/\partial c)$ and $(\partial \Delta S_{is}/\partial c)$ are constants due to the linearity (7).

The results of the statistical treatment of the B_i-parameters according to Eq. (9) by the method of linear least-squares are given in Table 2. A good linearity between the B_i parameters and the function 1/T is observed up to some maximum temperature (about 60°C). At higher temperatures the linear dependence is bent and has a much lower value of the slope . (See Fig. 1.).

Table 1.

The Results of the Statistical Treatment of the Activity Coefficients of Strong Electrolytes in Aqueous Solutions at Different Temperatures by the Least-Squares Method.

No	Electrolyte (temperature)	a_t	$\Delta \ln \gamma_\pm$	B_i	r^a	s^b	s_o^b	Ref.
1	2	3	4	5	6	7	8	9
1.	HCl							
	0°C	0.639	0.038± 0.002	0.423± 0.001	0.999	0.004	0.003	5
			0.032± 0.002	0.425± 0.001	0.999	0.006	0.003	6
	10°C	0.646	0.033± 0.002	0.414± 0.003	0.999	0.007	0.007	6
	15°C	0.650	0.042± 0.002	0.408± 0.001	0.999	0.004	0.003	5
	20°C	0.653	0.031± 0.002	0.405± 0.002	0.999	0.005	0.006	6

Table 1 continued

1	2	3	4	5	6	7	8	9
	30°C	0.663	0.033± 0.002	0.402± 0.003	0.999	0.007	0.007	6
	35°C	0.669	0.041± 0.003	0.391± 0.003	0.999	0.005	0.008	5
	40°C	0.673	0.033± 0.002	0.392± 0.003	0.999	0.007	0.007	6
	45°C	0.686	0.044± 0.004	0.387± 0.003	0.999	0.005	0.009	5
	50°C	0.692	0.035± 0.003	0.389± 0.003	0.999	0.008	0.009	6
	60°C	0.696	0.040± 0.002	0.372± 0.002	0.999	0.003	0.006	5
			0.037± 0.002	0.376± 0.003	0.999	0.006	0.007	6
2. NaOH								
	0°C	0.639	-0.120± 0.037	0.270± 0.010	0.998	0.036	0.036	6
	10°C	0.646	-0.087± 0.038	0.267± 0.010	0.997	0.037	0.037	6
	20°C	0.653	-0.050± 0.026	0.256± 0.007	0.999	0.025	0.026	6
	30°C	0.663	-0.014± 0.022	0.252± 0.006	0.999	0.021	0.023	6
	40°C	0.673	0.008± 0.019	0.245± 0.005	0.999	0.018	0.020	6
	50°C	0.692	0.026± 0.015	0.241± 0.004	0.999	0.014	0.016	6
	60°C	0.696	0.017± 0.011	0.234± 0.003	0.999	0.011	0.013	6
	70°C	0.707	0.024± 0.051	0.218± 0.013	0.993	0.049	0.061	6
3. KOH								
	0°C	0.639	0.032± 0.004	0.331± 0.002	0.999	0.009	0.006	6
	10°C	0.646	0.031± 0.004	0.341± 0.002	0.999	0.008	0.007	5

Table 1 continued

1	2	3	4	5	6	7	8	9
			0.038± 0.002	0.335± 0.001	0.999	0.006	0.004	6
	20°C	0.653	0.027± 0.004	0.338± 0.002	0.999	0.007	0.006	5
			0.036± 0.002	0.331± 0.001	0.999	0.004	0.003	6
	30°C	0.663	0.045± 0.002	0.333± 0.001	0.999	0.006	0.004	6
	40°C	0.673	0.018± 0.002	0.323± 0.001	0.999	0.003	0.003	5
	60°C	0.696	0.036± 0.002	0.316± 0.001	0.999	0.004	0.004	5
	80°C	0.722	0.033± 0.003	0.296± 0.002	0.999	0.005	0.005	5
4.	NaCl							
	0°C	0.639	0.024± 0.005	0.164± 0.002	0.999	0.008	0.012	6
	10°C	0.646	0.032± 0.003	0.181± 0.001	0.999	0.005	0.008	5
			0.029± 0.003	0.180± 0.001	0.999	0.005	0.007	6
	20°C	0.653	0.028± 0.003	0.190± 0.001	0.999	0.003	0.005	5
			0.027± 0.002	0.189± 0.001	0.999	0.003	0.005	6
	30°C	0.663	0.038± 0.002	0.201± 0.001	0.999	0.003	0.003	6
	40°C	0.673	0.040± 0.003	0.207± 0.002	0.999	0.006	0.007	5
	60°C	0.696	0.043± 0.006	0.220± 0.003	0.999	0.010	0.013	5
	80°C	0.722	0.046± 0.007	0.219± 0.003	0.999	0.012	0.015	5
			0.048± 0.006	0.219± 0.003	0.999	0.011	0.013	6

Table 1 continued

1	2	3	4	5	6	7	8	9
	90°C	0.734	0.047± 0.006	0.220± 0.003	0.999	0.011	0.013	5
	100°C	0.750	0.043± 0.007	0.221± 0.003	0.999	0.012	0.016	5
			0.057± 0.014	0.218± 0.007	0.996	0.027	0.030	6
5. NaBr								
	0°C	0.639	0.022± 0.005	0.209± 0.003	0.999	0.011	0.012	6
	10°C	0.646	0.029± 0.003	0.228± 0.002	0.999	0.006	0.007	5
			0.031± 0.003	0.228± 0.002	0.999	0.006	0.007	6
	20°C	0.653	0.026± 0.003	0.240± 0.001	0.999	0.005	0.006	5
			0.025± 0.002	0.240± 0.001	0.999	0.004	0.004	6
	30°C	0.663	0.034± 0.001	0.255± 0.001	0.999	0.002	0.001	6
	40°C	0.673	0.033± 0.002	0.263± 0.001	0.999	0.005	0.006	5
			0.033± 0.001	0.263± 0.001	0.999	0.003	0.002	6
6. KCl								
	0°C	0.639	0.022± 0.005	0.092± 0.003	0.996	0.010	0.030	6
	10°C	0.646	0.025± 0.001	0.107± 0.001	0.999	0.002	0.005	5
			0.025± 0.001	0.106± 0.001	0.999	0.001	0.003	6
	20°C	0.653	0.026± 0.002	0.111± 0.001	0.999	0.004	0.009	5
			0.024± 0.001	0.113± 0.001	0.999	0.001	0.004	6

Table 1 continued

1	2	3	4	5	6	7	8	9
	30°C	0.663	0.035± 0.002	0.123± 0.001	0.999	0.003	0.008	6
	40°C	0.673	0.035± 0.003	0.127± 0.002	0.999	0.006	0.012	5
			0.035± 0.003	0.129± 0.002	0.999	0.005	0.011	6
	50°C	0.692	0.012± 0.006	0.114± 0.010	0.973	0.015	0.086	7
7. KBr								
	25°C	0.660	0.036± 0.002	0.134± 0.001	0.999	0.004	0.009	5
	60°C	0.696	0.039± 0.006	0.171± 0.003	0.999	0.011	0.019	5
	70°C	0.707	0.041± 0.007	0.176± 0.004	0.999	0.012	0.020	5
	80°C	0.722	0.044± 0.008	0.181± 0.004	0.999	0.013	0.022	5
	90°C	0.735	0.045± 0.008	0.185± 0.004	0.999	0.014	0.022	5
	100°C	0.750	0.046± 0.008	0.189± 0.004	0.999	0.014	0.022	5
8. LiCl								
	0°C	0.639	0.047± 0.009	0.367± 0.005	0.999	0.018	0.014	5
	25°C	0.660	0.047± 0.010	0.356± 0.004	0.999	0.021	0.015	5
	50°C	0.692	0.048± 0.003	0.344± 0.001	0.999	0.005	0.004	5

[a] The correlation coefficient

[b] The standard deviation

[c] The normalized standard deviation

Table 2

The Results of the Statistical Treatment of the B_i Parameters According to Eq.(9) by the Least-Squares Method.

No	Electrolyte	$t^{o}(C)$	$\frac{\partial \Delta H_{is}}{\partial c}$ (kcal/mol)	$\frac{\partial \Delta S_{is}}{\partial c}$ (cal mol^{-1} deg^{-1})	r^{a}	s^{b}	s_o^{c}
1.	HCl	0 - 60	0.29 ± 0.02	-0.65 ± 0.05	0.986	0.003	0.053
2.	NaOH	0 - 60	0.22 ± 0.01	-0.27 ± 0.02	0.993	0.003	0.052
3.	KOH	0 - 80	0.22 ± 0.03	-0.58 ± 0.09	0.952	0.005	0.125
4.	NaCl	0 - 60	-0.33 ± 0.02	-1.88 ± 0.06	0.991	0.003	0.056
5.	NaBr	0 - 40	-0.45 ± 0.02	-2.49 ± 0.06	0.995	0.002	0.039
6.	KCl	0 - 50	-0.29 ± 0.02	-1.44 ± 0.07	0.986	0.002	0.068
7.	KBr	0 - 60	-0.32 ± 0.03	-1.65 ± 0.03	0.986	0.004	0.069
8.	LiCl	0 - 50	-0.16 ± 0.01	-0.89 ± 0.04	0.997	0.001	0.073

a - c cf. the corresponding footnotes of Table 1.

The coefficients $(\partial \Delta H_{is}/\partial c)$ and $(\partial \Delta S_{is}/\partial c)$ are linear for the alkali halides (a linear free energy relationship (LFER)). This linear relationship is characterized by the following parameters:

$$\frac{\partial \Delta H_{is}}{\partial c} = -(0.019 \pm 0.028) + (0.174 \pm 0.016) \frac{\partial \Delta S_{is}}{\partial c} \quad (10)$$

$$(r = 0.988, \quad s = 0.019, \quad s_o = 0.091)$$

The intercept of this relationship is equal to zero and therefore a proportionality between the parameters $(\partial \Delta H_{is}/\partial c)$ and $(\partial S_{is}/\partial c)$ is observed (see Fig. 2.). The LFER of this type is probably valid only for the electrolytes of the same valence type and similar structure, because the points for the acids, bases and $CaCl_2$ quite significantly deviate from relationship (10). The generalization of these LFER is presently restricted due to the absence of the corresponding data.

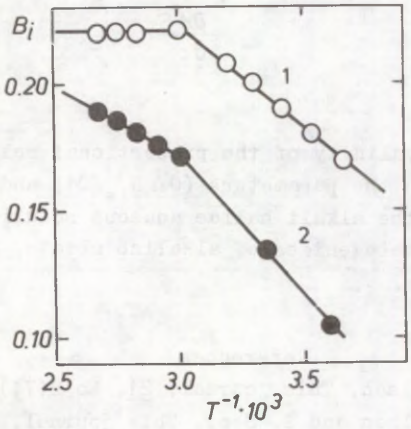

Fig. 1. The validity of the linear relationship (6) for some electrolytes in aqueous solutions. 1 - NaCl, 2 - KBr.

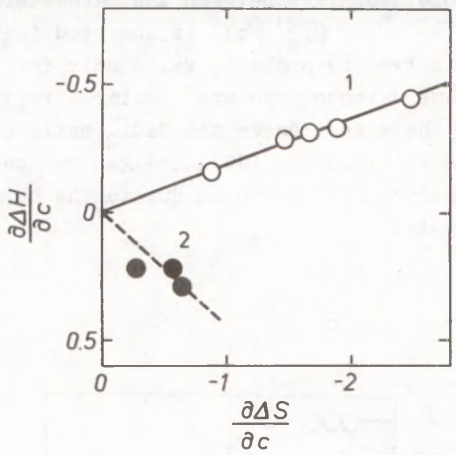

Fig. 2. The validity of the proportional relationship between the parameters $(\partial \Delta H_{is}/\partial c)$ and $(\partial \Delta S_{is}/\partial c)$ for the alkali halide aqueous solutions.
1 - halogenides of alkaline metals, 2 - acids and bases.

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STRUCTURAL THEORY OF ELECTROLYTE SOLUTIONS
V. ACTIVITY COEFFICIENTS OF STRONG ELECTROLYTES IN NON-AQUEOUS SOLUTIONS.

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The structural theory of electrolyte solutions proposed earlier by one of the authors[1] is verified on the basis of experimental activity coefficient data in non-aqueous solutions (methanol, ethanol, formamide, N-methylformamide, N-methyl acetamide). The results of the statistical treatment confirm the validity of this theory for several non-associated electrolytes in these solvents. The relationship between the solvent restructurization volumes, V_s, and the intrinsic structure of electrolyte is discussed.

There is a significant practical and theoretical interest in investigating the validity of the simple structural model of electrolyte solutions[1] in the case of non-aqueous solvents. According to this model the partial excess free energy of an electrolyte in the solution is given by the following formula:

$$\Delta G_{ex} = \Delta G_{el} + \Delta G_{is}, \qquad (1)$$

where ΔG_{el} denotes the electrostatic interionic interaction term and ΔG_{is} the term showing the electrolyte-solvent in-

teraction. The former is given by the following theoretical expression[2]:

$$\Delta G_{el} = \frac{24.7689}{\varepsilon} z_+ z_- \nu \sqrt[3]{\nu c}, \qquad (2)$$

where ε is the dielectric permittivity of the solvent, z_+ and z_- denote the ionic charges, ν is the number of ions in the electrolyte molecule and c - the molar concentration of the electrolyte in solution.

The partial excess free energy of the solute-solvent interaction has the following form:

$$\Delta G_{is} = 2\nu RTV_s c \ , \qquad (3)$$

where V_s denotes the specific volume of restructurization of the solvent by a given electrolyte. Proceeding from the formal relationship between the logarithm of the activity coefficient and the partial excess free energy, the following expression is valid for the activity coefficients of electrolyte in solution:

$$\ln f_{\pm} = \frac{24.7689}{\varepsilon RT} z_+ z_- \sqrt[3]{\nu c} + 2V_s c = a_t \sqrt[3]{c} + B_i c, \qquad (4)$$

where a_t is a theoretical constant, which depends only on the valence type of the given electrolyte, the temperature and the dielectric permittivity of the solvent, and B_i - a specific parameter for a given electrolyte in a given solvent.

The results of the statistical treatment of the experimental activity coefficient data for several electrolytes in different solvents (methanol, ethanol, formamide, N-methylformamide, N-methylacetamide) according to equation:

$$\ln f_{\pm} = \ln f_{\pm} + a_t \sqrt[3]{c} + B_i c \qquad (5)$$

are given in Table 1. The intercept $\Delta \ln f_{\pm}$ is introduced into the last formula because of the different standardization of the activity coefficients in the literature. (The experimental data are obtained from the handbooks[3,4]). The theoret-

ical values of the constant a_t for different solvents are also given in Table 1 . It should be mentioned that there is a good agreement between these theoretical numbers and the corresponding experimental slopes obtained from Eq.(5) in the case of electrolyte solutions in methanol, ethanol and formamide. In case of solutions in N-methylformamide and N-methylacetamide there is a larger scattering of the a_t values obtained from the statistical treatment. However, these solvents are characterized by the very high values of the dielectric permittivity (182.4 and 165.5, respectively), which leads to the small values of the parameter a_t. Therefore the exact estimation of this parameter is difficult because of the significant relative errors in the diluted solutions.

The statistical treatment of data also proceeded according to the simplified equation:

$$\ln f_{\pm} - a_t \sqrt{c} = \Delta \ln \nu_{\pm} + B_i c \,, \qquad (6)$$

where there is a known function in the left hand side, calculated using the theoretical value of a_t for a given solvent. The results of this treatment are given in Table 2.

We should like to mention that the values of the B_i parameters of the respective electrolytes are higher in alcoholic solutions in comparison with aqueous solutions (See[5]). The limited experimental data, however, do not allow to find any general relationship between the numerical values of these parameters in these solvents. On the other hand, the B_i-parameters for alkali halides in N-methylacetamide (MAA) are in satisfactory correlation with the corresponding parameters in water. This correlation is described by the following relationship:

$$B_i(\mathrm{MAA}) = (0.28 \pm 0.04) + (1.99 \pm 0.15) B_i(H_2O) \qquad (7)$$
$$(r = 0.988,\ s = 0.038,\ s_o = 0.076)$$

The slope of this linear relationship is larger than unity, i.e. the structure-formation ability of these electrolytes is higher in N-methylacetamide.

Table 1

The Results of the Statistical Treatment of the Activity Coefficients of Strong Electrolytes in Non-Aqueous Solutions According to Eq. (5) by the Least-Squares Method.

No	Electrolyte	$\Delta \ln f_{\pm}$	a_t	B_i	r^a	s^b	s_o^c
1	2	3	4	5	6	7	8
		1. Methanol (a_t(theor.)= -1.582)					
1.	HCl	0.02± 0.01	-2.02± 0.03	0.65± 0.05	0.999	0.010	0.007
2.	LiCl	0.13± 0.04	-1.73± 0.14	1.13± 0.14	0.990	0.030	0.061
3.	NaCl	0.06± 0.02	-1.58± 0.14	1.43± 0.07	0.997	0.017	0.037
4.	NaBr	0.07± 0.01	-1.86± 0.03	0.57± 0.02	0.999	0.010	0.01C
5.	KCl	0.08± 0.01	-1.54± 0.01	1.51± 0.06	0.999	0.007	0.022
6.	KBr	0.22± 0.03	-1.53± 0.12	4.48± 0.31	0.999	0.008	0.02C
7.	KI	0.10± 0.02	-1.60± 0.10	2.25± 0.18	0.986	0.025	0.062
8.	RbCl	0.09± 0.01	-1.61± 0.08	1.55± 0.39	0.999	0.007	0.019
9.	Pr_4NI	0.08± 0.01	-1.33± 0.02	0.25± 0.01	0.999	0.007	0.007
10.	Bu_4NI	0.14± 0.01	-1.71± 0.04	0.45± 0.03	0.999	0.013	0.012
		2. Ethanol (a_t(theor.)= -2.125)					
11.	HCl	-0.04± 0.04	-2.32± 0.07	0.62± 0.04	0.995	0.049	0.028
12.	HBr	-0.11± 0.05	-2.15± 0.03	2.76± 0.10	0.996	0.016	0.045
13.	NaBr	0.16± 0.01	-2.09± 0.08	2.09± 0.17	0.999	0.006	0.017

Table 1 continued

1	2	3	4	5	6	7	8
14.	NaI	$-0.08^{\pm}_{0.09}$	$-2.37^{\pm}_{0.22}$	$1.12^{\pm}_{0.12}$	0.985	0.095	0.042
15.	Pr_4NI	$0.21^{\pm}_{0.04}$	$-2.70^{\pm}_{0.13}$	$0.69^{\pm}_{0.16}$	0.999	0.020	0.018
16.	Bu_4NI	$0.21^{\pm}_{0.04}$	$-2.79^{\pm}_{0.10}$	$0.83^{\pm}_{0.06}$	0.998	0.033	0.020
		3. Formamide (a_t(theor.) = -0.472					
17.	HCl	$0.02^{\pm}_{0.01}$	$-0.37^{\pm}_{0.02}$	$0.47^{\pm}_{0.09}$	0.999	0.001	0.017
18.	NaCl	$0.08^{\pm}_{0.01}$	$-0.51^{\pm}_{0.03}$	$0.40^{\pm}_{0.03}$	0.997	0.002	0.033
19.	CsCl	$0.05^{\pm}_{0.01}$	$-0.50^{\pm}_{0.04}$	$0.16^{\pm}_{0.04}$	0.997	0.004	0.029
		4. N-Methylformamide (a_t(theor.)= -0.283)					
20.	LiCl	$0.01^{\pm}_{0.01}$	$-0.19^{\pm}_{0.01}$	$-1.85^{\pm}_{0.03}$	0.999	0.001	0.002
21.	NaCl	$0.06^{\pm}_{0.20}$	$-0.39^{\pm}_{0.09}$	$0.61^{\pm}_{0.25}$	0.973	0.004	0.094
22.	NaBr	$0.01^{\pm}_{0.01}$	$-0.19^{\pm}_{0.02}$	$0.04^{\pm}_{0.05}$	0.999	0.001	0.018
		5. N-Methylacetamide (a_1(theor.)= -0.294)					
23.	LiCl	$-0.02^{\pm}_{0.01}$	$-0.27^{\pm}_{0.04}$	$0.68^{\pm}_{0.07}$	0.999	0.004	0.028
24.	NaCl	$0.02^{\pm}_{0.01}$	$-0.21^{\pm}_{0.01}$	$0.68^{\pm}_{0.01}$	0.999	0.001	0.007
25.	NaBr	$-0.01^{\pm}_{0.01}$	$-0.14^{\pm}_{0.01}$	$0.72^{\pm}_{0.01}$	0.999	0.002	0.006
26.	NaI	$0.01^{\pm}_{0.01}$	$-0.34^{\pm}_{0.01}$	$0.94^{\pm}_{0.01}$	0.999	0.002	0.002
27.	KBr	$-0.13^{\pm}_{0.01}$	$-0.20^{\pm}_{0.01}$	$0.50^{\pm}_{0.01}$	0.999	0.001	0.003

Table 1 continued

1	2	3	4	5	6	7	8
28.	CsI	$0.01^{\pm}_{0.01}$	$-0.16^{\pm}_{0.01}$	$0.36^{\pm}_{0.13}$	0.999	0.001	0.023
29.	$LiNO_3$	$0.02^{\pm}_{0.01}$	$-0.25^{\pm}_{0.01}$	$0.82^{\pm}_{0.01}$	0.999	0.001	0.004
30.	$NaNO_3$	$0.02^{\pm}_{0.01}$	$-0.21^{\pm}_{0.01}$	$0.08^{\pm}_{0.01}$	0.999	0.001	0.004
31.	Me_4NCl	$-0.01^{\pm}_{0.01}$	$-0.12^{\pm}_{0.02}$	$-0.11^{\pm}_{0.02}$	0.999	0.002	0.024
32.	Et_4NCl	$-0.01^{\pm}_{0.01}$	$-0.11^{\pm}_{0.02}$	$0.20^{\pm}_{0.02}$	0.995	0.004	0.038
33.	Pr_4NCl	$-0.01^{\pm}_{0.01}$	$-0.13^{\pm}_{0.01}$	$0.31^{\pm}_{0.01}$	0.999	0.003	0.015
34.	Bu_4NCl	$-0.01^{\pm}_{0.01}$	$-0.09^{\pm}_{0.02}$	$0.36^{\pm}_{0.02}$	0.999	0.004	0.015
35.	Et_4NBr	$0.01^{\pm}_{0.01}$	$-0.16^{\pm}_{0.01}$	$-0.15^{\pm}_{0.01}$	0.999	0.002	0.008
36.	Pr_4NBr	$0.03^{\pm}_{0.01}$	$-0.27^{\pm}_{0.01}$	$-0.01^{\pm}_{0.01}$	0.999	0.002	0.009
37.	Bu_4NBr	$0.03^{\pm}_{0.01}$	$-0.27^{\pm}_{0.01}$	$0.08^{\pm}_{0.01}$	0.999	0.002	0.016
38.	HCOOLi	$0.06^{\pm}_{0.01}$	$-0.32^{\pm}_{0.05}$	$-0.18^{\pm}_{0.07}$	0.999	0.005	0.024
39.	CH_3COOLi	$0.02^{\pm}_{0.01}$	$-0.23^{\pm}_{0.01}$	$-0.32^{\pm}_{0.01}$	0.999	0.001	0.004
40.	C_2H_5COOLi	$0.01^{\pm}_{0.02}$	$-0.27^{\pm}_{0.01}$	$-0.20^{\pm}_{0.01}$	0.999	0.001	0.005

[a] The correlation coefficient

[b] The standard deviation

[c] The normalized standard deviation

Table 2.

The Results of the Statistical Treatment of the Activity Coefficients of Strong Electrolytes in Non-Aqueous Solutions According to Eq. (6) by the Least-Squares Method.

No	Electrolyte	$\Delta \ln f_{\pm}$	B_i	r[a]	s[b]	s_o[c]
1	2	3	4	5	6	7
		1. Methanol				
1.	HCl	-0.06 ± 0.10	-0.01 ± 0.07	0.043	0.043	0.289
2.	LiCl	0.09 ± 0.01	0.99 ± 0.05	0.994	0.033	0.045
3.	NaCl	0.06 ± 0.01	1.46 ± 0.21	0.991	0.015	0.038
4.	NaBr	-0.03 ± 0.07	0.38 ± 0.02	0.983	0.025	0.049
5.	KCl	0.08 ± 0.01	1.77 ± 0.16	0.980	0.006	0.088
6.	KBr	0.12 ± 0.01	2.38 ± 0.07	0.999	0.008	0.014
7.	KI	0.010 ± 0.01	2.21 ± 0.06	0.997	0.024	0.028
8.	RbCl	0.08 ± 0.01	1.42 ± 0.10	0.983	0.007	0.070
9.	Pr_4NI	0.16 ± 0.01	0.40 ± 0.02	0.991	0.020	0.039
10.	Bu_4NI	0.09 ± 0.01	0.38 ± 0.01	0.996	0.017	0.028
		2. Ethanol				
11.	HCl	-0.07 ± 0.01	0.27 ± 0.01	0.995	0.042	0.028
12.	HBr	-0.12 ± 0.01	2.66 ± 0.20	0.986	0.014	0.075

Table 2 continued

1	2	3	4	5	6	7
13.	NaBr	0.16± 0.01	2.16± 0.04	0.999	0.001	0.020
14.	NaI	-0.04± 0.06	2.02± 0.09	0.985	0.207	0.042
15.	Pr_4NI	0.38± 0.26	0.03± 0.11	0.122	0.044	0.444
16.	Bu_4NI	-0.06± 0.03	0.44± 0.04	0.984	0.071	0.096
		3. Formamide				
17.	HCl	0.04± 0.01	0.89± 0.05	0.992	0.002	0.056
18.	NaCl	0.04± 0.01	0.30± 0.01	0.997	0.004	0.030
19.	CsCl	0.04 ± 0.01	0.14± 0.01	0.985	0.004	0.063
		4. Methylformamide				
20.	LiCl	0.03± 0.01	-1.57± 0.02	0.999	0.001	0.014
21.	NaCl	0.04± 0.01	0.32± 0.05	0.924	0.004	0.144
22.	NaBr	0.03± 0.01	0.31± 0.02	0.984	0.001	0.073
		5. Methylacetamide				
23.	LiCl	0.51± 0.01	1.09± 0.07	0.994	0.015	0.063
24.	NaCl	0.04± 0.01	0.81± 0.02	0.999	0.005	0.027
25.	NaBr	0.05± 0.01	0.86± 0.02	0.998	0.011	0.020
26.	NaI	0.05± 0.01	1.06± 0.01	0.999	0.010	0.012

Table 2 continued

1	2	3	4	5	6	7
27.	KBr	0.04±0.01	0.62±0.02	0.998	0.006	0.028
28.	CsI	0.04±0.01	0.53±0.02	0.996	0.008	0.047
29.	$LiNO_3$	0.04±0.01	0.87±0.01	0.999	0.010	0.048
30.	$NaNO_3$	0.04±0.01	0.15±0.01	0.989	0.004	0.018
31.	Me_4NCl	0.05±0.01	0.09±0.03	0.827	0.014	0.203
32.	Et_4NCl	0.06±0.01	0.36±0.02	0.990	0.010	0.049
33.	Pr_4NCl	0.06±0.01	0.44±0.01	0.996	0.020	0.042
34.	Bu_4NCl	0.06±0.01	0.53±0.02	0.995	0.013	0.031
35.	Et_4NBr	0.05±0.01	-0.04±0.01	0.793	0.016	0.251
36.	Pr_4NBr	0.04±0.01	0.01±0.01	0.805	0.003	0.188
37.	Bu_4NBr	0.04±0.01	0.09±0.01	0.996	0.003	0.028
38.	HCOOLi	0.02±0.01	-0.34±0.03	0.986	0.013	0.068
39.	CH_3COOLi	0.04±0.01	-0.23±0.01	0.993	0.009	0.082
40.	C_2H_5COOLi	0.04±0.01	-0.10±0.03	0.916	0.009	0.159

a - b cf. the corresponding footnotes of Table 1.

An interesting relationship between the B_i-parameters and the intrinsic volumes of organic electrolytes is also observed in the case of N-methylacetamide. The intrinsic volumes of electrolytes are estimated on the basis of the cor-

responding bond refractions ($\sum R_D$). For the electrolyte series Alk_4NCl, where Alk denotes an alkyl substituent, the following equation is valid (V_s scale is used (cm^3/mol)):

$$V_s = (67.7 \pm 5.7) + (2.15 \pm 0.09) \sum R_D \qquad (8)$$

$(r = 0.998,\ s = 3.60,\ s_o = 0.040)$

For the electrolyte series Alk_4NBr:

$$V_s = (-120.9 \pm 18.2) + (1.75 \pm 0.24) \sum R_D \qquad (9)$$

$(r = 0.991,\ s = 6.25,\ s_o = 0.135)$

and for the series $H(CH_2)_nCOOLi$ $(n = 0, 1, 2)$

$$V_s = (-265.5 \pm 7.6) + (12.94 \pm 0.60) \sum R_D \qquad (10)$$

$(r = 0.999,\ s = 3.98,\ s_o = 0.047)$

The validity of such relationships confirms the structural model used in the derivation of the basic formula (3), since there is a straightforward correlation between the size of organic electrolyte and the volume of that restructurized by it solvent. The different intercepts exist due to the different structurization volumes of the counterions in the molecules of organic electrolytes. The slopes of relationships (8) and (9) for tetraalkylammonium chlorides and bromides, respectively, are close but essentially smaller than the slope of relationship (10) for the lithium carboxylates. The latter is in good agreement with the corresponding slope for sodium carboxylates in aqueous solutions (12.53 ± 0.16[1]). This may be caused by the similar mechanism of the influence on the solvent structure by the anions. However, the different sensitivity to the intrinsic structure evidences about the difference in this influence by the organic ions of opposite charge type.

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TEMPERATURE EFFECTS ON THE DIFFERENTIAL CONDUCTOMETRIC MEASUREMENTS

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The results of the differential conductometric measurements of the influence of small non-electrolyte additions on the electrical conductivity of strong electrolyte (NaCl, LiCl), solutions in water and isoamyl alcohol at 18°, 25° and 35°C are presented. The temperature effects on the solvent structurization parameters V_s are discussed.

In the previous communications[1-4] the results of the differential-conductometric investigation of the non-electrolyte effects on the structure of the strong electrolyte aqueous and non-aqueous solutions were given.

In the differential conductometry the quantity

$$Y = \frac{k \cdot 10^3}{c_s} \left(\frac{1}{R_o + \Delta R} - \frac{1}{R_x} \right) \qquad (1)$$

is studied. In this formula k denotes the cell constant (cm^{-1}), c_s is the molar concentration of the non-electrolyte addition to the electrolyte solution, R_o and R_x are the resistances (Ω) of this solution before and after adding non-electrolyte to the solution, respectively. The term ΔR takes into account the change in the resistance of the solution because of the dilution in the process of addition.

It was shown by us[1], that the quantity Y is simply related to the volume of structurization V_s of the solvent by the given non-electrolyte addition according to the follow-

ing formula:

$$Y = V_s \cdot \varkappa \quad , \qquad (2)$$

where $\varkappa$ denotes the specific conductivity of the electrolyte solution. The molar volume V_s corresponds to that part of the total volume of solution, where the dynamic properties of ions have been changed. In the case of positive V_s values, the ions are converted from the conducting state to the non-conducting state, and in the case of negative V_s values, the opposite process is observed. In general, the parameter V_s characterizes the specific interaction between the non-electrolyte addition and solvent.

In the previous investigations[1-4], the differential conductometric effect was studied at the constant temperature (25°C). However, the structure of liquids and solutions is rather sensitive to the temperature changes. Therefore the parameter V_s should be temperature-dependent, too.

In the present work the results of the differential-conductometric measurements of the influence of small additions of ethanol, isobutyl alcohol, isoamyl alcohol and acetonitrile on the conductivity of sodium chloride aqueous solutions and of the influence of small additions of water, ethanol and isobutyl alcohol on the conductivity of lithium chloride in isoamyl alcohol on the conductivity of lithium chloride in isoamyl alcohol at 18°, 25° and 35°C are given. It should be mentioned that due to the significant temperature-dependence of the ionic conductivity itself, the precise thermostating is needed in the differential conductometry ($\pm$0.001°C). Therefore it is difficult to extend these measurements to the wider range of temperature.

Experimental.

Ethanol (grade "Pure for analysis") was dried on CaO and distilled. The fraction used had b.p. 78.4°C and d_{25}^{25}= 0.7898.

Isobutyl alcohol (grade "Pure ") was distilled. The fraction used had b.p. 107.5°C, d_{25}^{25} = 0.8019 and n_D^{20}= 1.3960.

Isoamyl alcohol (grade "Pure") was distilled. The fraction used had b.p. 130.5°C, d_{25}^{25} = 0.8123 and n_D^{20}= 1.4080.

Acetonitrile (grade "Pure for analysis") was mixed with KOH and distilled. The main fraction obtained was treated with CaH_2 and distilled. The fraction used had b.p. 101.5°C (760 mm Hg) and $d_4^{20} = 1.0329$.

The water used was deionized and bidistilled. The differential-conductometric measurements were made on the apparatus described elsewhere[8]. The conductivity cell was isolated from the surrounding atmosphere by the CaO tubes to prevent the absorption of water. The cell constant was $k = 19.40\ cm^{-1}$. A constant resistance $R_p = 9907.0\ \Omega$ was used in parallel joint to the conductivity cell for the investigation of dilute solutions of electrolytes characterized by the low conductivity values. The dilution correction ΔR in Eq. (1) was calculated according to the procedure given elsewhere[2].

Discussion.

The numerical values of the quantity Y for different non-electrolyte additions to the electrolyte solutions in water and isoamyl alcohol are given in Tables 1-6. These data were treated by the least-squares method according to the following equation

$$Y = V_s \mathcal{C} + a_o, \qquad (3)$$

where a_o denotes a small intercept due to the conductivity of addition. The parameters of this treatment for every individual non-electrolyte addition are presented in Tables 7 and 8.

It should be noted that the monotonic decrease of the V_s values is observed parallel to the increase of temperature (See Figs.1. and 2.)

According to the two-structure model of solutions used in the derivation of Eq. (1)[1], it corresponds to the decrease of the restructurization power of the additions. This is equally true for the structure-formation and structure-breaking effects. The former is observed in the case of organic non-electrolyte additions to the NaCl aqueous solutions and the latter - in the case of hydroxylic additions to the LiCl

Table 1

Differential-Conductometric Quantities Y for the Additions of Ethanol and Isobutyl Alcohol to the Aqueous Solutions of NaCl at 18°C.

c_{NaCl} (M)	$\varkappa$ ($\Omega^{-1}cm^{-1}$)	Y	
		ethanol	isobutyl alcohol
0.378	0.0312	4.2	6.4
0.774	0.0592	8.4	9.9
1.066	0.0777	9.7	16.4
1.125	0.0812	10.5	17.8
2.439	0.1482	22.7	28.8
3.391	0.1776	25.3	44.0
3.952	0.1925	27.7	47.1
4.803	0.2091	25.3	51.9

Table 2.

Differential-Conductometric Quantities Y for the Additions of Ethanol and Isobutyl Alcohol to the Aqueous Solutions of NaCl at 35°C.

c_{NaCl} (M)	$\varkappa$ ($\Omega^{-1}cm^{-1}$)	Y	
		ethanol	isobutyl alcohol
0.370	0.0433	4.4	7.2
1.034	0.1022	10.9	16.9
1.255	0.1236	13.9	18.1
1.892	0.1564	13.6	22.9
2.375	0.1968	19.7	36.4
2.804	0.2221	22.2	37.8
3.728	0.2590	26.9	43.0

Table 3

Differential-Conductometric Quantities Y for the Additions of Isoamyl Alcohol and Acetonitrile to the Aqueous Solutions of NaCl at 18°C.

c_{NaCl} (M)	$\varkappa$ ($\Omega^{-1}cm^{-1}$)	Y	
		isoamyl alcohol	acetonitrile
0.144	0.0127	3.4	0.7
0.399	0.0327	7.1	1.7
0.987	0.0712	19.1	4.4
1.002	0.0738	21.5	4.8
1.590	0.1070	27.4	7.3
2.143	0.1355	35.9	12.4
2.617	0.1558	39.1	14.4
3.294	0.1760	50.5	18.4
3.988	0.1941	53.1	19.7

Table 4

Differential-Conductometric Quantities Y for the Additions of Isoamyl Alcohol and Acetonitrile to the Aqueous Solutions of NaCl at 35°C

c_{NaCl} (M)	$\varkappa$ ($\Omega^{-1}cm^{-1}$)	Y	
		isoamyl alcohol	acetonitrile
0.278	0.0332	5.1	2.5
0.567	0.0630	12.3	2.7
1.013	0.1020	21.4	4.0
1.633	0.1491	25.6	7.7
2.135	0.1835	29.3	8.6
2.757	0.2169	38.2	12.1
2.858	0.2245	44.1	13.5

Table 5.

Differential-Conductometric Quantities Y for the Additions of Water, Ethanol and Isobutyl Alcohol to the Solutions of Lithium Chloride in Isoamyl Alcohol at 18°C.

c_{LiCl}(M)	$\varkappa \cdot 10^3$ ($\Omega^{-1}cm^{-1}$)	Y . 10^3		
		water	ethanol	isobutyl alcohol
0.018	0.0143	-	-7.0	0.1
0.057	0.0374	-21.8	-	-
0.086	0.0514	-	-21.3	-6.2
0.103	0.0588	-29.9	-	-
0.154	0.0782	-50.4	-34.4	-12.8
0.222	0.1006	-57.9	-	-
0.239	0.1050	-	-42.2	-21.8
0.249	0.1089	-58.1	-	-
0.377	0.1411	-61.5	-50.5	-21.2
0.389	0.1447	-	-53.1	-26.2
0.438	0.1554	-84.4	-	-
0.693	0.2172	-	-82.9	-26.5
0.789	0.2444	-	-84.8	-36.5
0.875	0.2695	-129.0	-	-

Table 6.

Differential-Conductometric Quantities Y for the Additions of Water, Ethanol and Isobutyl Alcohol to the Solutions of Lithium Chloride in Isoamyl Alcohol at 35°C.

c_{LiCl}(M)	$\varkappa \cdot 10^3$ ($\Omega^{-1}cm^{-1}$)	Y . 10^3		
		water	ethanol	isobutyl alcohol
1	2	3	4	5
0.041	0.0305	-	-18.1	-3.6
0.086	0.0628	-	-26.8	-7.2
0.114	0.0823	-48.1	-	-
0.129	0.0925	-	-40.2	-11.6
0.134	0.0959	-55.2	-	-
0.156	0.1112	-55.3	-	-

Table 6 continued

1	2	3	4	5
0.191	0.1335	-91.9		
0.194	0.1351	-	-53.6	-12.1
0.221	0.1520	-	-61.1	-17.2
0.242	0.1658	-99.0	-	-
0.298	0.1982	-	-70.4	-21.0
0.400	0.2533	-128.0	-	-
0.438	0.2727	-	-85.3	-22.5
0.491	0.2972	-154.2	-	-
0.510	0.3066	-	-108.0	-30.9
0.570	0.3311	-175.1	-	-
0.583	0.3365	-	-115.2	-28.8
0.882	0.4135	-201.0	-	-
0.852	0.4203	-	-141.1	-46.6

Table 7.

The Results of the Least-Squares Treatment of the Differential-Conductometric Data for the Aqueous Solutions of NaCl.

Non-electrolyte addition	t(°C)	a_o	V_s (cm^3/mol)	r^a	s^b	s_o^c
1 2	3	4	5	6	7	8
1. Ethanol	18°C	-0.8 ± 0.8	148.3 ± 6.6	0.995	1.0	0.04
	35°C	-1.4 ± 2.0	99.4 ± 9.4	0.978	1.7	0.09
2. Isobutyl alcohol	18°C	-3.5 ± 2.0	256.4 ± 14.2	0.991	2.6	0.05
	35°C	-1.5 ± 1.7	172.8 ± 8.7	0.992	1.9	0.05
3. Isoamyl alcohol	18°C	-1.1 ± 1.4	276.5 ± 11.3	0.994	2.0	0.04
	35°C	-1.1 ± 2.9	186.9 ± 18.5	0.976	3.2	0.09

Table 7 continued

1	2	3	4	5	6	7	8
4.	Acetonitrile	18°C	-2.3± 1.2	109.4± 8.8	0.975	1.8	0.08
		35°C	-2.2± 1.7	63.9± 9.4	0.950	1.6	0.14

a The correlation coefficient

b The standard deviation

c The normalized standard deviation

Table 8.

The Results of the Least-Squares Treatment of the Differential-Conductometric Data for the Solutions of LiCl in Isoamyl Alcohol.

Non-electrolyte addition	t(°C)	$a_o \cdot 10^3$	V_s (cm^3/mol)	r^a	s^b	s_o^c
1. Water	18°C	-13.3± 5.1	-738.9± 36.8	0.991	7.2	0.049
	35°C	13.4± 8.7	-482.3± 36.6	0.980	12.3	0.074
2. Ethanol	18°C	-3.1± 5.0	-386.3± 40.6	0.974	6.7	0.102
	35°C	8.5± 2.7	-319.5± 11.4	0.995	4.4	0.035
3. Isobutyl alcohol	18°C	-0.2± 2.8	-143.0± 9.6	0.956	4.1	0.131
	35°C	4.6± 2.1	-85.5± 9.0	0.959	3.5	0.100

a - c The corresponding footnotes at Table 7.

solutions in isoamyl alcohol (positive and negative values of V_s, respectively).

The results obtained in the present work are in accordance with the structural theory of electrolyte solutions[9], because the increase of the thermal mobility of solution particles leads to the decrease of the intrinsic structure of solution and also to the decrease of the restructurized

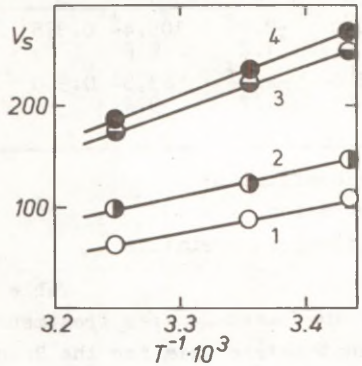

Fig. 1. The temperature dependence of V_s values for several compounds in the aqueous solutions of NaCl (1-acetonitrile, 2-ethanol, 3-isobutyl alcohol, 4-isoamyl alcohol).

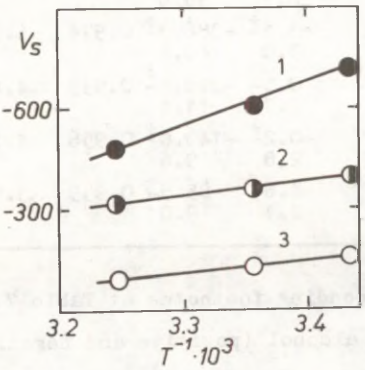

Fig. 2. The temperature dependence of V_s values for several compounds in the solutions of LiCl in isoamyl alcohol (1-water, 2-ethanol, 3-isobutyl alcohol).

zones around the solute molecules. The slope of the temperature dependence of V_s-parameters increases as the absolute value of V_s increases for a non-electrolyte addition at a given temperature. This means that the outer shells of the restructurized solvent around the solute particle are more sensitive to the temperature effects, i.e. the solvent molecules there are more easily converted to the unperturbed state corresponding to the pure solvent.

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REALIZATION OF THE GENERAL ALGORITHM OF THE SOLUTION OF DIRECT PROBLEMS FOR HOMOGENEOUS EQUILIBRIUM-KINETIC MECHANISTIC SCHEMES.

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The algorithm is described for solution of chemical kinetic problems for arbitrary mechanistic schemes which reflect reaction systems consisting of fast equilibria and nonreversible or reversible rate limiting stages. The corresponding system of differential and algebraic equations is formed automatically. The algorithm is realized and proved as an ANSI-77 FORTRAN program for computer NORD 100 (NORSK DATA, Norway).

Introduction

The direct problem of chemical kinetics is defined as a complete description of the composition of the multicomponent system at the arbitrary time moment. This is possible in principle if the values of all parameters to be used are known. For the homogeneous system at constant tem-

perature, pressure and volume these parameters are rate or equilibrium constants and initial concentrations of components.

The kinetics of complex chemical reactions is described by a system of first order differential equations which relate the rates of the change of the components concentrations to their current concentrations. A set of the algebraic equations should be added to reflect the very fast equilibria and the stationary relations between some of the components. The terms "fast equilibria" and "stationary" are relative since they depend on the time moment after the reaction has been started. The solution of these equations cited at any time moment represents the solution of the direct problem.

There is no general analytical solution for the systems cited. Nevertheless, the real solution of these problems of moderate step of complexity is possible if digital approach is employed making use of computers. The algorithms described for this purpose either require the explicit definition of subprocedures to reflect the essence of every new mechanistic scheme [1] or the problems are restricted to the systems of either fast equilibria [2-6] (system of algebraic equations) or rate limiting steps [7-12] (system of differential equations). So there remains a problem of the solution for a combined set of fast and slow stages without a necessity to prepare new special program units.

Although ,in principle, all fast equilibrium steps can be substituted by reversible rate determining ones if the

values of corresponding rate constants are known, such kind of information is usually unavailable. Besides that, the essential application field of the algorithm under consideration is its application as a function to be parametrized when the reverse problem must be solved. That means the estimation of the equilibrium and rate constants values by the use of a set of the corresponding experimental data. The nature of the latter frequently requires introduction into the mechanistic scheme either fast equilibria or stages in the case of which the stationarity conditions are held.

These were the reasons why we set a goal to elaborate a general enough algorithm for solution of combined kinetic-equilibrium problems via the modification of known methods in this field. The requirements are that the composition as well as the modification of the systems of algebraic and differential equations during the solution procedure should be done automatically. A computer program based on such an algorithm enables one to formulate any special problem to be solved via corresponding set of initial data without taking care about additional program units to be prepared and loaded. This program could be used as a function for (nonlinear least square) parametrization procedure to test arbitrary, in principle, mechanistic models proceeding from the corresponding experimental data.

Description of Algorithm

The solution of any problem of the studied type has to be started from the construction of a corresponding mechanistic model - a set of processes. The elementary processes

of the model are characterized by the corresponding independent parameters - rate and equilibrium constants.

This model is represented by a set of stoichiometric equations for reactions (all terms are represented on the right side of equations, resulting in zero value on the left hand side):

$$0 \rightleftharpoons \sum_{j=1}^{s} \alpha_{ij} A_j \; ; \quad i = 1,\ldots,r \; ,$$

where A_j denote reactants and α_{ij} is the stoichiometric coefficient before A_j in the i-th reaction.

The stoichiometric coefficients are of positive sign for final products and negative - for the initial ones.

These equations could be represented by the stoichiometric matrix $//\alpha_{ij}//$ 13/. If the vector-column $//A_j//$ is formed from the symbols of reactants, the system of stoichiometric equations may be represented as follows:

$$0 = //\alpha_{ij}//*//A_j//$$

Here and further the asterisk * denotes multiplication.

As an example for the mechanistic scheme represented by two parallel processes as follows:

$$A + B \rightleftharpoons C$$

$$A + 2B \rightleftharpoons D$$

the matrix equation could be written as follows:

$$0 = \begin{vmatrix} -1 & -1 & 1 & 0 \\ -1 & -2 & 0 & 1 \end{vmatrix} * \begin{vmatrix} A \\ B \\ C \\ D \end{vmatrix}$$

The mathematical model for a chemical system is based on the equations for equilibrium constants and formal kine-

tics. The values of the so called dependent parameters should be added. The values of the latter (initial concentrations, temperature, pressure etc.) may be varied deliberately by the experimenter. The equations used reflect the mass (charge) preservation law or the mass action law. Conventionally they are cited as the equations of the material balance (MB) and mass action law (MAL), respectively.

The set of MB and MAL equations for the current equilibrium state (fast equilibria are considered) constitute a system of nonlinear algebraic equations. This system has always only a single positive real solution [14]. For the solution of such systems of equations several methods are suggested [2-6,15]. They differ from each other by the nature of parameters varied as well as by the method of solution. Most of those methods are discussed in detail in paper [6].

As already mentioned above, in principle one can avoid application of algebraic equations for equilibria and solve a system of differential equations for a set of processes represented by the rate determining ones, only [*]. In reality there arise difficulties in the course of the digital integration of the corresponding systems of differential equations due to their "rigidity". By the last term is meant

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[*] If the value of the equilibrium constant is known for the rate constant of reverse reaction arbitrary enough high value could be assigned and the value of the rate constant of the direct reaction calculated.

arising of the situation where in some range of the solution small changes of concentrations lead to large changes of the reaction rates. For chemical systems the "rigidity" is caused by great differences in rate constant values. As a result in some cases the concentrations close to equilibrium values are reached while the others are rather far from those values.From the point of view of calculation technique such kind a situation arises when the integration range is determined by the value of the smallest rate constant but the integration step depends on the largest one. Therefore the solution algorithm becomes unacceptably time consuming [16]. A number of algorithms avoiding this difficulty has been described [7-11] and the detailed analysis of this problem has been published [12,16].

The substitution of a part of differential equations by the algebraic ones is reasonable if in the time range studied, some of the reactions or components reach their equilibrium state or stationary concentration, respectively. This seems to be a most natural way for avoiding the calculation difficulties arising from the "rigidity" phenomenon.

The very fast equilibria may be introduced into the initial model itself as well as some stationary concentrations. This is lawful if the assumed rates of the corresponding elementary processes are by several powers of magnitude faster than those characteristic of the time range considered. It has to be stated once more that in the case of the solution of reverse (parametrization) problems this approach has a principal advantage. Indeed, it may appear

that the estimation of the rate constants for such reactions proceeding from the available experimental data, is actually impossible. This is the very reason why the automatic solution of the direct problem for a mechanistic scheme with instantly reached equilibria and pseudostationary concentrations becomes practically important.

The algorithm described in this communication enables the solution of the system of algebraic and differential equations formed for any special case of the direct problem. In order to use the digital methods of solution this system is divided into subsystems of differential and algebraic equations, respectively. It can be pictured as a sequential realization of slow (kinetic) and fast (equilibrium) stages in a given system of reactions. The general algorithm contains, correspondingly, two basic subprocedures granting the calculation of the current equilibrium and stationary concentrations and the determination of the depth of conversion for slow reactions, respectively.

Further the identificators will be used as follows:

NA - total number of equilibrium stages

ND - total number of kinetic stages

ND2 - total number of reversible kinetic stages

ND1 - total number of nonreversible kinetic stages

NC - total number of components (all ingredients whose concentrations are taken into account in the course of the solution process)

NW - total number of basic concentrations

IST - total number of quasistationary concentrations

Z(L) - extent of conversion for the L-th kinetic stage

AC(J) - initial concentration of the J-th component

C(J) - current concentration of the J-th component

X(I) - the I-th rate or equilibrium constant

NS(M) - the sequency number (J value) for the M-th stationary concentration

M(I,J) - the element of the stoichiometric matrix (the stoichiometric coefficient for the J-th component in the I-th reaction)

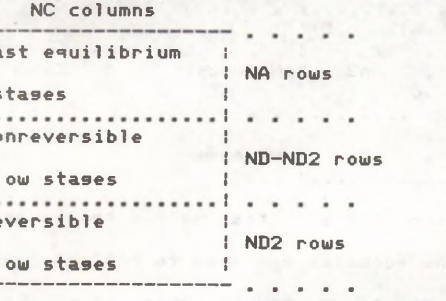
EP - the relative precision criterion of the solution of the algebraic equations

EPDIF - the same for differential equations

EPSTA - the same for calculation of stationary concentrations

The stoichiometric matrixes describe all reactions for a given system. The initial stoichiometric matrix contains columns for all components of the system. The first NA rows correspond to fast equilibrium reactions. The following ND - ND2 rows correspond to the nonreversible and the last ND2 ones to reversible slow reactions.

The shape of the initial stoichiometric matrix can be illustrated by the following scheme:



For example, the stoichiometric matrix and the corresponding mechanistic scheme describe a system with 5 components involved into two fast equilibria, a nonreversible and a reversible slow stages:

```
   A B C D E   (components)     A + B ⇌ D          fast equi-
 .............                  A + 2B ⇌ C + E      libria
 | -1 -1 0 1 0 |    NA = 2
 | -1 -2 1 0 1 |
 |  0 1 0 0 -1 |    ND = 2       E ---> D          slow
 |  0 0 -1 1 0 |
 !.............!    ND2=1        C ⇐===⇒ D         steps
```

During the solution process, the equations for the fast equilibria are transformed in such a way that the obtained system corresponds to a set of reactions with at least one component on the right side for each of them not present on the right side of all other reactions. It means that for a transformed set each reaction leads to the formation of at least one component not formed in any other reaction of the set.

This transformation reduces the "equilibrium component" of the stoichiometric matrix to a diagonal form that can be illustrated as follows:

```
                .
   NC-NA columns .NA columns
 ..............................  .  .  .
 !                .n1      0  !
 !                .  n2       !
 !                .    n3     ! NA rows
 !                .0       .  !
 ..................  ........!  .  .  .
 !                .           !
 !                .    0      ! ND rows
 !..............................!  .  .  .
```

17

For transformation of the initial matrix the Gauss method is emplоyed. The formulas are used to reflect the algebraic addition of a single row to all others to obtain the

zero value for the element with given index values *:

$$M(I,JJ)' = M(I,JJ) - M(L,JJ).M(I,J)/M(L,J) \quad ; \qquad (1)$$

I=1,NA+ND; J=NC-NA,NC; L=1,NA; JJ=1,NC

M(I,JJ)' and M(I,JJ) denote the new and old values of the I-th element of the JJ-th column; L is the index of the row to be added to all other ones in order to obtain zero values for the J-th elements of these rows.

To preserve the reaction system defined initially it is necessary also to change the definitions of the equilibrium constants. For this purpose the formula is used as follows:

$$X(I)' = X(I)/(X(L))^{M(I,J))/M(L,J)} \quad ; \qquad (2)$$

I = 1,NA+ND; L = 1,NA; J = NC-NA+1,NC

To grant integer values for the stoichiometric coefficients in the transformed matrix, in case the M(I,J) value can not be divided to the M(L,J) one without reminder, formulae (1) and (2) must be substituted by the following ones:

$$M(I,JJ)' = M(I,JJ).M(L,J) - M(L,JJ).M(I,J) \quad , \qquad (3)$$

$$X(I)' = X(I)^{M(L,J)}/X(L)^{M(I,J)} \quad ; \qquad (4)$$

JJ = 1,NC; L = 1,NA; I = 1,NA+ND; J=NC-NA+1,NC

According to the observed algorithm, the obtained stoichiometric matrix is transformed, by means of interchange of its columns, to the state where the main diagonal

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*/

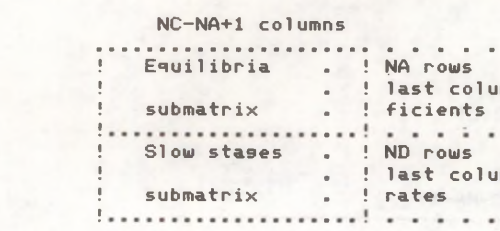
The ranges of the changes of indexes are marked in "fortrane-like" way.

elements of the submatrix with dimensions NA*(NC-NA) (located in the upper right-hand part) all have nonzero values. The components which correspond to the first NA (if NA > NC-NA then first NC-NA) columns of the matrix obtained will be cited further as the basic ones. In the course of solution only the basic components concentrations are varied. Concentrations of the remaining components are calculated proceeding from the basic ones making use of the MAL and MB equations.

The specific structure of the part of algorithm designed for the calculation of equilibrium concentrations leads to the requirement that the initial stoichiometric concentrations for nonbasic components should not be included into the set of initial data. If this rule is violated from the very beginning, the corresponding automatic procedure will be introduced to express the initial stoichiometric concentrations of the nonbasic components via those for the basic ones. The initial data are recalculated to be represented by a set which includes the initial stoichiometric concentrations for the basic components only. When calculating the initial concentration of the basic component, the expressions for the initial concentrations of nonbasic components are used in the sequence of their presence in the stoichiometric matrix. If on the running step of that substitution the negative value is obtained, the set of basic components has to be changed. During the execution of the program the corresponding message is output on the terminal. After that the initial data should be reprepared proceeding from a different set of basic components.

The compact form of the transformed matrix is then used for further operations. A single column with index value NC--NA+1 is substituted for last NA columns. The first NA elements of this column are equal to the diagonal elements of the quadratic right-hand part of the submatrix for equilibria. They are equal to the stoichiometric coefficients of nonbasic components of the corresponding reactions. Other elements, related to the slow stages, are cited further as the "powers of reaction rates". Usually they equal unity. A different value for the power of the I-th reaction is obtained if necessary to use the formulae (3) and (4) during the transformation of the matrix. In that case the I-th element of the last column is equalized with the absolute value of the J-th element of the L-th row M(L,J). The latter is now the value of the power of the I-th reaction.

The final form of the transformed and compact stoichiometric matrix corresponds to the scheme as follows:



The solution procedure of the system of equations for equilibria is devoted to the calculation of the running concentrations of corresponding components for each given set of the depths of kinetic stages. The latter is a result of the integration procedure of the system of differential equations (on the running step).

The equations of the corresponding algebraic system result from the corresponding MB and MAL equations.

The MB equations are as follows:

$$C(K) = AC(K) + \sum_{I=1}^{NA} M(I,K)*C(I+NC-NA)/M(I,NC-NA+1) + \sum_{L=1}^{ND} M(L+NA,K)*Z(L) \quad ; \quad K=1,NW \qquad (5)$$

The MAL equations could be represented as follows:

$$C(I+NC-NA) = \sqrt[M(I,NC-NA+1)]{\prod_{J=1}^{NC-NA} C(J)^{-M(I,J)}} * X(I) \quad ; \quad I=1,NA \qquad (6)$$

After inserting equation (6) into (5) and elimination of the C(I+NA-N) term the system of NW equations is as follows:

$$C(K) = (AC(K) + S1)/(1. + S2) \quad , \quad K=1,NW \ , \qquad (7)$$

where:

$$S1 = \sum_{L=1}^{ND} (M(L+NA,K)*Z(L) \ ,$$

$$S2 = \sum \left[Y(I) * \sqrt[M(I,NC-NA+1)]{\prod_{J=1}^{NC-NA} X(I) * C(KT(J))^{-M(I,J)}} \right] \quad ; \quad J \neq K,$$

$$Y(I) = M(I,K)*C(K)^{-(1+M(I,K)/M(I,NC-NA))/M(I,NC-NA)}$$

This system is solved making use of the modified Seidels iteration procedure [18]. Modification is introduced to damp down the vibration of the solution. If for two subsequent iteration steps the opposite changes of the solution for a given concentration result the next approximation is equalized with the arithmetical mean between two last estimated approximations of this concentration. If

Sign(C(K);n-1 - C(K);n) =/= Sign(C(K);n -C(K);n+1),

then the assignement is made as follows:

C(K);n+1 = (C(K);n+1 + C(K);n)/2. ,

where C(K);n-1, C(K);n and C(K);n+1 denote the solutions of the given inexplicit equation (7) for three last iteration steps, respectively. The iterative process is continued up to the conversgence of all concentrations accordings to the precision criterion EP. This is indicated by the satisfaction of the followings condition:

Abs [(C(K);n+1 - C(K);n)/C(K);n] < EP ; K=1,NW .

Each subsequent inexplicit equation of the system is solved for estimation of the next approximation of C(K);n+1 (the concentration of the K-th component) making use of the modified chords method [19]. The solution is defined as the crossing point of the straight line Y = X of the identity relationship with the function which represents the form (in general a hyperbolic one) of the right- hand side of the equation to be solved.

The corresponding iterative algorithm constructed works as follows. Let us mark the values of the hyperbolic function for the last two iteration steps by f(x;n-1) and

f(x;n),respectively (x;n-1 and x;n are the corresponding concentrations). The next approximation x;n+1 can be calculated using one of the three possible versions:

i) If f(x;n > x;n then x;n+1 =

= [x;n-1*f(x;n)-x;n*f(x;n-1)]/[f(x;n)-f(x;n-1)-x;n+x;n-1]

ii) If f(x;n) < x;n then x;n+1 = f(x;n)

iii) If f(x;n) < 0 then x;n+1 = (x;n-1 + x;n)/2.

If for the initial approximation f(x;1) < 0 and x;1 > > 0, the value x;1 = 2.*x;1 is assigned. But if x;1 = 0 the reassignement x;1 = 20.*EP is the case.

The iterative process is continued up to the conversing according to the precision criterion EP reflected by the satisfaction of the relation:

Abs [(f(x;n) - x;n)/x;n] < EP.

Two types of differential equations are present in the system. For irreversible reactions they are as follows:

$$\partial Z(L)/\partial t = \left(X(L+NA)*\prod_{J=1}^{NW} C(J)^{-M(L+NA,J)} \right)^{1/M(L+NA,NW+1)} ;$$

$$L = 1,ND1 \; ; \quad -M(L+NA,J) > 0 \; . \qquad (8)$$

For reversible processes the equations are as follows:

$$\partial Z(L)/\partial t = \left(X(N)*\prod_{J=1}^{NW} C(J)^{-M(L+NA,J)} \right)^{1/M(L+NA,NW+1)} +$$

$$- \left(X(N+1)\prod_{JJ=1}^{NW} C(JJ)^{M(L+NA,JJ)} \right)^{1/M(L+NA,NW+1)} ; \qquad (9)$$

L=ND1+1,ND.

Where N = 2L+NA-ND-1 (-M(L+NA,J) and M(L+NA,JJ) > 0).

At t=0 for all components formed from the initial ones

$$Z(L) = 0 \; ; \; L=1,ND \; .$$

For integration of this system of differential equations the method of Runge-Kutta[20] is used.

The system of differential equations described can be represented as follows:

$$\partial Z(L)/\partial t = F(L)(Z(1),\ldots,Z(ND)); \; L=1,ND.$$

The integration formulae are as follows:

$$Z(L)(t+Dt) =$$

$$= Z(L)(t) + Dt*[F1(L)+2*F2(L)+2*F3(L)+F4(L)]/6, \quad (10)$$

where

$$F1(L) = F(L)(Z(1)(t),\ldots,Z(ND)(t))$$

$$F2(L) = F(L)(Z(1)(t)+Dt*F1(1)/2,\ldots,Z(ND)(t)+Dt*F1(ND)/2)$$

$$F3(L) = F(L)(Z(1)(t)+Dt*F2(1)/2,\ldots,Z(ND)(t)+Dt*F2(ND)/2)$$

$$F4(L) = F(L)(Z(1)(t)+Dt*F3(1),\ldots,Z(ND)(t)+Dt*F3(ND)),$$

Dt denotes the integration step and t - the time moment at the beginning of the current integration step.

If the integration version up to the precision required is employed, the repeated reduction of Dt by the half is executed up to the satisfaction of the relation:

$$Abs \; [\; (Z(t+Dt)-Z((t+Dt/2)+Dt/2))/Z(t+Dt) \;] < EPDIF$$

When the execution of the next integration step starts, the Dt value is multiplied by a constant[1,2] for the sake of the economy of the computer time within the assigned precision limits.

If the "rigidity" cited above arises, it is considered as a sign of the satifaction of the quasistationarity condition in respect to a single or more components. To enchan-

ce the rate of the integration process with the precision required, the vibration of the running values of the calculated quasistationary concentrations should be suppressed. This is done via the change of the calculation of quasistationary concentrations using the corresponding algebraic equations (using the Bodenstein method). The condition of the quasistationarity is expressed as follows:

$$\partial C(st)/\partial t \simeq 0 \qquad (11)$$

where C(st) denotes the stationary concentration.

The rate of the change of quasistationary concentration could be expressed as a difference between the rates of formation and further transformation of the corresponding component. Therefore the condition of quasistationarity in respect to the K-th component can be defined as follows:

$$\partial C(K)(st)/\partial t = \sum_{I=NA+ND-ND2}^{NA+ND-ND2} [\, M(I,K)*X(I)*\prod_{J=1}^{NW} C(J)^{-M(I,J)} \,] + \sum_{I=NA+ND-ND2}^{NA+ND} [\, M(I,K)*X(2I-NA-ND-1)*\prod_{J=1}^{NW} C(J)^{-M(I,J)} - X(2*I-NA-ND)*\prod_{JJ=1}^{NW} C(JJ)^{M(I,JJ)} \,] \quad ; K=NS(IJ),\ IJ=1,IST \qquad (12)$$

$$\{\ M(I,J) > 0 \ \text{ and } \ M((I,JJ) > 0\ \}$$

Consequently, for the stationary concentration of the K-th component the following expression can be derived:

$$C(K)(st) = (S1 + S2)/(S3+S4)\ , \qquad (13)$$

where

$$S1 = \sum_{IS=NA+1}^{NA+ND-ND2} [\, M1(IS,K)*X(IS)*\prod_{J=1}^{NC-NA} C(J)^{-M(IS,J)} \,]$$

$$S2 = \sum_{IL=NA+ND-ND2+1}^{NA+ND} \left[M2(IL,K)*X(N)*\prod_{J=1}^{NC-NA} C(J)^{M2(IL,J)} \right]$$

$$S3 = \sum_{IJ=NA+1}^{NA+ND-ND2} \left[M3(IJ,K)*X(IJ)*\prod_{J=1}^{NC-NA} C(J)^{-M(IJ,J)} \right]$$

$$S4 = \sum_{IM=NA+ND-ND2+1}^{NA+ND} \left[M4(IM,K)*X(P)*\prod_{J=1}^{NC-NA} C(J)^{M4(IM,J)} \right]$$

where $-M(IS,J) > 0$ and $-M(IJ,J) > 0$.

If $M(IS,K) > 0$, then M1(IS,K)=M(IS,K) ,

else M1(IS,K)=0

If $M(IJ,K) > 0$, then M3(IJ,K)=-M(IJ,K),

else M3(IS,K)=0

If $M(IL,K) < 0$, then M2(IL,K)=-M(IL,K) and N=2*IL-NA-ND,

else M2(IL,K)= M(IL,K) and N=2*IL-NA-ND-1.

If M2(IL,K) <0 and M(IL,J) >0

or M2(IL,K) >0 and M(IL,J) <0

then M2(IL,J) = Abs (M(IL,J)]

else M2(IL,J) = 0 .

If $M(IM,K) > 0$, then M4(IM,K)=M(IM,K) and N=2*IL-NA-ND,

else M4(IM,K)=-M(IM,K) and N=2*IL-NA-ND-1.

If M4(IM,K) <0 and M(IM,J) <0

or M4(IM,K) >0 and M(IM,J) >0

then M4(IM,J) = Abs (M(IM,J)]

else M4(IM,J) = 0 .

Equations (12) and (13) are then the correct ones if the condition (11) is satisfied.

For the check of the quasistationarity of a given component, the current concentration values of that calculated by means of a routine procedure and using formula (13) are compared. If the first one begins to vibrate around the second one the condition of the quasistationarity for a given component is considered to be satisfied. Further the current concentration of this component will be calculated according to formula (10). As an indicator of the necessity of the check of the quasistationarity condition serves the occurrence of the negative value for the current concentration of the corresponding component. If several interrelated quasistationary concentrations are present, the corresponding system of equations (13) is solved using the Seidel method with the modifications cited above.

During the solution procedure the incompatibilities between the concentrations of components calculated applying equations (13) (C(K)(st)) and (5) (C(K)(MB) according to the mass action law) may crop up. Such a contradiction to the law of the conservation of matter is removed by artificial change of reaction depths if the corresponding component is consumed or formed. The depths of reactions are varied proportionally to the rates of conversion of components in the corresponding reactions for a current time moment. For the positive or negative value of the difference C(K)(st) - C(K)(MB) the current depths are corrected for reactions, the given component is an initial or final product, respectevely. This correction is made by solution of the system of equations in respect to Z(I); I=1,ND:

$$C(K)(st)\{ Z(1)+\Delta Z(1),\ldots,Z(ND)+\Delta Z(ND) \} =$$

$$= C(K)(MB)\{ Z(1)+\Delta Z(1),\ldots,Z(ND)+\Delta Z(ND) \} .$$

If

$$C(K)(st)\{ Z(1),\ldots,Z(ND) \} < C(K)(MB)\{ Z(1),\ldots,Z(ND) \},$$

and $M(I+NA,K) < 0$, or

$$C(K)(st)\{ Z(1),\ldots,Z(ND) \} > C(K)(MB)\{ Z(1),\ldots,Z(ND) \},$$

and $M(I+NA,K) > 0$, then

$$\partial\Delta Z(I)/\left[\sum_{L=1}^{ND} Z(L)\right] = Y*[\,\partial(Z(I)+\Delta Z(I))/\partial t\,] \qquad (14)$$

else $Z(I) = 0.$ $I = 1,ND$.

Equations (14) of this system are approximately equivalent to the next one actually used in the algorithm:

$$\Delta Z(I)/[\,\partial Z(I)/\partial t + \partial(Z(I)+\Delta Z(I))/\partial t\,] = Y \ (=const) \qquad (14a)$$

The initial values for $Z(I)$ are of zero value. For Y the initial approximation is defined by expression:

$$Yo = \frac{C(K)(st)\{ Z(1),\ldots,Z(ND)\} - C(K)(MB)\{ Z(1),\ldots,Z(ND)}{\underset{L=1}{\overset{ND}{\mathrm{Max}}}\,[M(I,K)*\partial Z(L)/\partial t]}$$

The system of equations

$$\Delta Z(I) = Y*[\,\partial Z(I)/\partial t + \partial(Z(I)+\Delta Z(I))/\partial t\,] \ ; \ I=1,ND$$

is solved making use of the Seidel method up to the satisfaction of the condition:

$$abs\,[\Delta Z(I)(n) - \Delta Z(I)(n-1)\,]/\Delta Z(I)(n) < EPDIF \ ; \ I=1,ND$$

Then the subsequent approximation is calculated:

$$Y(n+1) = Y(n)/(1 - R1/R2),$$

where

$$R1 = C(K)(st)\{ Z(1)+\Delta Z(1),\ldots,Z(ND)+\Delta Z(ND) \} +$$
$$- C(K)(MB)\{ Z(1)+\Delta Z(1),\ldots,Z(ND)+\Delta Z(ND) \}$$
$$R2 = C(K)(st)\{ Z(1),\ldots,Z(ND) \} - C(K)(MB)\{ Z(1),\ldots,Z(ND) \}$$

The iteration process is continued up to the satisfaction of the condition:

$$Abs [Y(n+1) - Y(n)]/Y(n+1) < EPDIF$$

After satisfaction of this relation new values are assigned to all depths of reactions:

$$Z(I)(new) = Z(I)(init) + \Delta Z(I) \ ; \ I=1,ND$$

The system of equations (14) is solved one by one for all stationary concentrations in the case of which the condition is not satisfied as follows:

$$Abs [C(K)(st)\{Z\} - Z(K)(MB)\{Z\}]/C(K)(st) < EPSTA \quad (15)$$

If the condition (15) for stationary concentration is not satisfied for two subsequent steps of integration, the corresponding component is excluded from the set of stationary concentrations.

The fast equilibriums as well as stationary concentrations could be postulated preliminarily and included into the reaction scheme. If not the absolute values but only a number of combinations of some of the rate constants (Michaelis or inhibitor binding apparent constants etc.) are known, it is natural to postulate the corresponding stationary states in the reaction scheme. For the corresponding rate constants involved one can assign arbitrary values which satisfy the known values of their combinations.

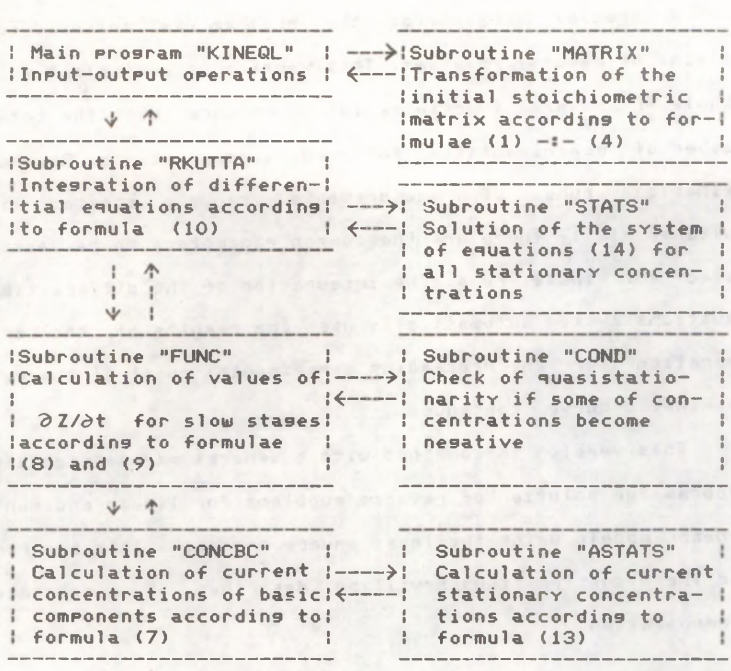


Fig. 1.

The General Block Scheme of the Program.

Realization of the Algorithm and Possible Applications

The program according to the algorithm described is written in FORTRAN. The information exchange with files is operated according to the version ANSI-77. Program is translated and checked making use of the computer NORD 100 (NORSK DATA, Norway).

The general functional structure of this program can be illustrated by the scheme represented in Fig. 1.

A special version of the program is adjusted for solving of reverse problems. This version is equivalent to a single or several functions, in accordance with the total number of experimentally followed concentrations. Several (kinetic) runs of measurements can be treated simultaneously if there are the common parameters to be estimated for these runs. The integration of the differential equations system automatically uses the results of the integration for the preceeding experimental point if the same kinetic curve continues.

This version is combined with a general parametrization program for solution of reverse problems for linear and nonlinear models using the least square approach. This program and the algorithm it uses will be described in a separate communication.

Besides the solution of direct and reverse problems in the narrow sense of this term, the program described could be used for the hypothetical modelling of the qualitative behavior of complex physico-chemical and biochemical systems.

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